PRODUCT LICENSING FRAMEWORK II
September 1997

DRAFT

Therapeutic Products Programme
Health Canada

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EXECUTIVE SUMMARY

Product Licensing Framework II proposes to re-design of the Canadian drug regulatory system by introducing a scheduled post-approval drug assessment program and integrating pre and post-approval review into a comprehensive program of ongoing pharmacovigilance. The licensing framework consists of two major components:

1. Pre-market drug product categorization, product licensing and assignment of reporting schedules

2. Post-approval surveillance*, licence renewal and amendment of reporting schedule.

Together these two components provide for a continuum of drug product evaluation from the time a product is received as a pre-market submission through to the time the drug product is no longer available on the market. Both components are based on risk management principles to ensure that the balance of benefits and risks for drug products with higher risk potential or identified safety concerns will be more intensely and continually monitored.

* Within this document, the term surveillance is used in a very comprehensive manner to encompass a variety of post-approval activities within the product licensing framework including: adverse drug reaction monitoring, risk/benefit assessment of post-approval reports, review of epidemiology studies and post-approval studies etc.

INTRODUCTION

Background

In August 1993, the Drugs Directorate, now the Therapeutic Products Programme (TPP), adopted and began to implement a renewal strategy to streamline the review and approval process for drugs in Canada. The impetus for this renewal strategy came from Dr. Denis Gagnon's review of the Canadian drug approval system which resulted in the 1992 report, *Working in Partnerships...drug review for the future*. In his report, Dr. Gagnon said that "it is time for us to come out of our traditional model (of drug review), and adopt the more efficient one which will allow us to do the job, within the limits of our resources." and that "an effective program of pharmacovigilance (be developed) as the second major lever of our drug approval system."

One of the outcomes from the implementation of the renewal strategy which responded to many of the recommendations from Dr. Gagnon's report was "A New Drug Licensing Framework for Canada". This document was released by the Therapeutic Products Programme for comment in January 1996. Following an internal impact assessment and a review of comments received from clients and stakeholders, the document was revised and renamed: Product Licensing Framework (PLF).[1]

In June 1997, an invitational technical workshop was held to gain further input on the scientific content of the document. Comments and input received at this workshop are reflected in this latest version of the document: Product Licensing Framework II.

Goals of the Product Licensing Framework

The Product Licensing Framework describes a renewed drug regulatory process which maintains and enhances current review standards for safety, quality and efficacy.

The goal of the Therapeutic Products Programme has been to develop a Product Licensing Framework that:
•integrates pre-market and marketed drug assessment into regulatory decision-making
•improves process efficiency
•achieves international harmonization

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1 [1]The Product Licensing Framework applies only to drug products that are regulated by the Therapeutic Products Programme. Medical devices are not currently included within the scope of the Product Licensing Framework.

Features of the Product Licensing Framework

The Product Licensing Framework consists of two major components:

1.Pre-market drug product categorization, data submission elements, licensing and assignment of post-approval reporting requirements.

2.Post-approval surveillance and product assessment, product/substance re-assessment, licence renewal and amendment of reporting requirements.

Together, these two components provide for a continuum of drug product evaluation from the time a product is received as a pre-market submission through to the time that the drug product is no longer available on the market. Both components of the continuum are based on benefit-risk principles.

Within PLF, risk refers to the available knowledge/experience relating to the quality, safety and efficacy of the drug product and/or identified product safety concerns. Drug products for which the TPP has little or no knowledge or experience or products that have identified safety issues will be considered to be potentially high risk.

Drug products with potentially high risks will require the highest level and most comprehensive pre-market data submission, will receive more intense pre-market scrutiny and will have a higher level and frequency of post-approval surveillance. Drugs of low risk will have minimal pre-market requirements and scrutiny and post-market assessment for these products will be based on signals arising from adverse event reports. The introduction in the framework of a scheduled post-approval assessment program for potentially high risk products will ensure that the balance of benefits and risks for a drug product are continually monitored.

Outcomes of Product Licensing

The changes to the drug regulatory process that are proposed in the Product Licensing Framework will enable the Therapeutic Products Programme to:

•continually monitor drug products with potential or identified safety concerns

•streamline the drug regulatory process and ensure competitive performance targets

•create a transparent process that is easy to understand and provides clear guidance to process participants both internal and external

•harmonize regulatory requirements with those agreed upon internationally

•integrate principles of quality management into the drug regulatory process

Each of the two major components of the Product Licensing Framework will be described separately, (Section 1, Pre-market; Section 2, Post-Approval) in comprehensive detail to facilitate a clear understanding of requirements within each of the components.

SECTION 1PRE-MARKET DRUG CATEGORIES, DATA SUBMISSION ELEMENTS, LICENSING AND ASSIGNMENT OF REPORTING SCHEDULES

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1.1Pre-Market Drug Categories and Data Submission Elements

1.1.1Introduction

The Therapeutic Products Programme (TPP) regulates a wide spectrum of products as drugs, ranging from toothpaste and antiperspirants that are available directly to consumers in grocery stores, pharmacies or health food stores to new active substances (pharmaceutical and biological) intended for prescription use only in highly specialized medical settings. Although the range of products is broad, and there are differences in risk posed and variability in data needs for making risk/benefit decisions, there are sufficient common factors among the drug products to allow grouping according to potential risk and general data needs. The Product Licensing Framework (PLF), groups all drug products into four broad categories (IV-I) ranked in **descending** order of risk as defined by the amount of knowledge/experience of quality, efficacy and safety or known risk available on the drug product. The general data elements that are required for appropriate benefit/risk decisions are commensurate with the categories of risk. On this basis, a new chemical entity about which there is no knowledge/experience on quality, safety and efficacy would be considered highest risk (Category IV). Such a drug product would require the most comprehensive pre-market data package to fully demonstrate quality, efficacy and safety and would receive a high level of pre-market review prior to market authorization. For products such as antiperspirants and toothpastes, the knowledge base and experience about quality safety and efficacy of the active ingredients is extensive and the risk that these products pose is considered minimal. Such products would be designated to Category I where the pre-market data submission and level of scrutiny would be considerably reduced.

The categorization of drug products does not introduce new pre-market activities but represents a repackaging, change of nomenclature and redefinition of all of the pre-market groupings and activities currently conducted. The approach described in the PLF will replace most of the existing regulations, policies and guidelines applicable to pre-market activity and make obsolete some of our current difficult nomenclature such as old drug/ new drug designation. New regulations, policies and guidelines will be developed to support the changes.

The four pre-market drug categories, the risk criteria and some examples of drug products within each category are summarized below:

Category IV - is for a drug product for which there is generally little prior experience or knowledge regarding the safety, efficacy or quality aspects of the active ingredient(s) or the non-medicinal ingredients. Examples of products in this class would include a new

vaccine or a new active substance. A new propellant in a metered dose inhaler would classify as a Category IV non-medicinal ingredient.

Category III - is for a drug product for which there is some prior experience or knowledge regarding the safety, efficacy and quality aspects of the active ingredient(s) of the drug product. Examples would include a product previously licensed in Canada presented as a new route of administration or new dosage form.

Category II - is for a drug product for which there is extensive prior experience or knowledge regarding the safety, efficacy and quality aspects of the active ingredient(s). Examples include shampoo for treatment of head lice and many of the marketed cough and cold medicines.

Category I - is for products for which extensive prior knowledge and experience regarding the safety, efficacy and quality aspects of the active ingredient(s) is available. Products within this category must meet a set of specific criteria designed to demonstrate minimal risk. The criteria are fully described later in this document in the section pertaining to Category I products. Examples of products in this category include: Antiperspirants, Athletes Foot Treatments, Sunburn Protectants.

Each of the four categories is further divided into subgroups based on the active ingredient, route, form or use of the drug product. General, broad pre-market data elements outlined for each category are commensurate with the potential risk of the products within that category. Accordingly, Category IV (highest risk, little or no prior knowledge) requires comprehensive data elements and will receive the highest level of pre-market scrutiny while Category I (lowest risk, extensive knowledge) will require no data submission but sponsors must provide attestation to compliance with a Class Monograph. Categories II and III have intermediate levels of necessary data elements consistent with the knowledge base and risk profile of the drug products within each group.

1.1.2Drug Product Categories: Subgroups and Data Elements

1.1.2.1Data Elements: General Overview

The complete data elements for pre-market submissions for categories IV, III and II products are grouped together in 14 tables and 1 form at the end of Section 1. Since Category I products do not have data elements, they are omitted from the tables; a listing of available Class Monographs is provided in the section describing Category I products.

Sponsors should note that the listed data elements are intended to be flexible and mirror current pre-market practices in the Therapeutic Products Programme. Because the drug categories contain broad groupings of products, the general data elements listed for each category are necessarily at the highest common level to ensure that the Programme can obtain the comprehensive data essential for decision making. For example, Table I lists all of the pre-market data that are recognized internationally as necessary to facilitate a risk/benefit decision for a Category IV new active (pharmaceutical) substance. However, it is recognized that some of the pre-clinical safety studies listed on that table may not be applicable to a new biological product. Accordingly, sponsors should use the tables as guides for data elements that are necessary for risk/benefit decisions about their products.

The pre-market data elements have been taken from several sources including current guidelines and policy statements. Footnotes attached to the tables refer to documents that provide more detailed information on data specifications.

The data elements are grouped into five major sections:

- Section I, *General Pre-market Data Elements*
- Section II, *In Vitro and Animal Studies*;
- Section III, *Human Studies*;
- Section IV, *Clinical Studies*; and
- Section V, *Chemistry and Manufacturing Data Elements*

Within each of these five major sections are subheadings that include more detailed data elements. Further instructions on how to use the tables are provided as a foreword to the tables at the end of Section 1.

It is important to remember that the data elements attached to each subgroup apply to that subgroup only. When more than one subgroup applies to a drug product (i.e. new indication and a new dosage form), then the elements for each applicable subgroup must be fulfilled.

The following sections describe individually, each of the four drug product categories, their subgroups and the types of drugs that fall within each category/subgroup. Each category/subgroup is followed by a box indicating which tables and/or forms to use to determine the submission data elements and any necessary additional information to facilitate decisions for drug products within that subgroup.

1.1.2.2Category IV Products: Subgroups and Data Elements

Sponsors must submit a Category IV data package for a drug product for which there is generally little prior experience or knowledge regarding the safety, efficacy or quality aspects of the active ingredient(s) or non-medicinal ingredients. In these cases, the Therapeutic Products Programme has little flexibility to waive data or information requirements because there is insufficient precedent to make such waiver decisions. Therefore, the sponsor must submit substantial information and data in all areas *for all Subgroup products except subgroup 4, and substantial information respecting safety and efficacy for Subgroup 4 products* so that the Programme can conduct an appropriate benefit-risk analysis.

The following are the Category IV subgroups representing drug products that contain an *active ingredient, indication for use or new combination* not previously licensed as a drug in Canada. Subgroup IV-6 is specific to novel non-medicinal ingredients.

Subgroup IV-1

The product contains a new active substance that is:

a)a chemical or biological substance not previously licensed for sale as a drug in Canada; or,

b)a biological substance previously licensed for sale as a drug in Canada which differs in molecular structure, nature of the source material or manufacturing process, and differing in properties with regard to safety and efficacy from that previously licensed biological substance.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

Complete the elements of Sections I, II, III, IV and V.

Subgroup IV-2

The product contains an active ingredient that is a derivative, isomer or salt of a chemical substance previously licensed for sale as a drug in Canada. It is recognized that in many instances, some of the necessary data elements for this subgroup will be met by information submitted previously for the original chemical substance. Where relevant, cross-referencing to the previously submitted data is recommended (see under data elements below). However, this subgroup is maintained in Category IV for the cases when a derivative, isomer or salt may have a substantially different safety and efficacy profile and where the Programme would require comprehensive supporting data for the new form. A classic example are the diasteriomers quinine and quinidine: quinine is an antimalarial whereas quinidine is a cardiac depressant.

There are numerous other examples which demonstrate that enantiomers may possess widely different toxicological, pharmacological and/or clinical properties (e.g. verapamil, timolol, thalidomide). In the case of thalidomide, one enantiomer is a sedative, the other a teratogen.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

Although the complete data elements listed on Table 1 apply, the safety and efficacy of the new derivative, salt or isomer of the active ingredient may be supported by a cross-reference to data submitted for the original active ingredient. Re-analyse the data in the original submission to determine areas of compatibility between the original and new drug products. Use Table 1 as a checklist.

Where information in a previous submission does not support, by itself, the safety and efficacy of the new active ingredient, sponsors may have to submit bridging studies to ensure the validity of cross-references.

Note: The Therapeutic Products Programme will require that the information available for a drug product under Subgroup IV-2 be as comprehensive as that necessary to assess a new active substance in Subgroup IV-1.

Subgroup IV-3

The product contains an active ingredient that is a plant or of plant origin that has not been previously licensed for sale in Canada and is not marketed within the scope of the *Therapeutic Products Directorate Guidelines: Traditional Herbal Medicines.* This subgroup is for plant extracts and plant products that are intended to be marketed as drugs with specific indications for which there is no history of use as a food or a traditional herbal medicine and for which the quality, safety and efficacy profile is completely unknown. Taxol (paclitaxel) is an example of a drug product that would classify to this subgroup.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

Complete the elements listed in Sections I, II, III, IV and V.

Subgroup IV-4

The product contains a chemical or biological substance that has been previously licensed for sale in Canada and the product is presented for a new indication that results in a change, in relation to the indication of the previously licensed product comparable to the first, second or third level of the Anatomical Therapeutic Chemical (ATC) classification code. An immunosuppressant with an original indication in organ transplantation presented for a new indication in the treatment of rheumatoid arthritis would classify to this category and subgroup.

Note: The ATC classification code is being used solely as a standard reference for determining the extent of change represented by the new indication. A change at the first level of the ATC classification system would mean the change in indication at the level of the anatomical system (i.e. change from nervous system to musculo-skeletal system). Changes at the second ATC level would denote change in the main therapeutic use of the drug (i.e. previous indication as psycholeptic, new indication anaesthetic); and, a change at the third level, would represent a change in the therapeutic subgroup (i.e. previous indication anti-psychotic, new indication hypnotic/sedative). A change comparable to the first, second or third level is considered a major change in indication and requires the appropriate pre-clinical and clinical supporting data. Where appropriate, cross-referencing to previously submitted relevant data is encouraged (see below under data requirements).

Data Elements

***Use*Section 1: Table 1--General Pre-market Data Elements**

Complete the data elements listed in Sections I, II, III and IV; and

Cross-reference a previous submission to Section V.

Note: Data needs for Subgroup IV-4 are limited exclusively to a change involving the indication. If other changes have been made to the product such as a revised dosage form, the submission must also include any additional requirements specified under subgroup III-4b.

Subgroup IV-5

The product contains active ingredients that are chemical or biological substances previously licensed for sale in Canada that are contained in a combination that has not been previously licensed for sale in Canada. It is recognized that this subgroup captures a broad spectrum of potential combination products. The data elements listed are set at the highest level to ensure the necessary data submission for combinations involving new actives for which quality, safety and efficacy profiles must be demonstrated. This subgroup will also encompass combination products involving two well characterized drug products about which there is much experience and knowledge. However, it cannot be assumed that individual therapeutic agents in combination drugs act independently in the biological system. The combined effects could be synergistic, antagonistic or even entirely new and could generate significant safety or efficacy concerns. For these types of combination products flexibility on data elements may be considered if there is substantial supportive data that the combination does not represent quality, safety or efficacy issues. In cases where such data is not available, the necessary information will need to be generated.

Data Elements

***Use*Section 1: Table 1--General Pre-market Data Elements** ***and*Section 1: Table 2--Pre-market Data Elements for Subgroup IV-5: A new combination of active ingredients**

Complete the data elements listed on Table 1, Sections I, II, III and IV.

Information may have been submitted previously for one or more of the active ingredients with regard to Table 1, Section V. For example, if sponsors have already submitted the method of manufacture of one or more of the raw materials and this information is still valid for the raw material in this product, sponsors may cross-reference the original information rather than resubmitting the information.

Other areas of the chemistry and manufacturing data that may be cross-referenced are indicated in the shaded areas in Table 2, Section V.

Subgroup IV-6

The product contains one or more non-medicinal ingredients (NMI) that have not been previously contained in a drug product licensed for sale in Canada. The level of risk associated with a new excipient is similar to that of a new drug substance and internationally, regulatory authorities generally do not approve the use of new excipients in a drug product without full toxicology and pharmacology studies and adequate information about its behaviour in clinical situations. Replacements for CFC propellant in a metered dose inhalers and polymeric excipients emerging from liposome technology serve as examples of excipients which require extensive data elements to demonstrate quality, safety and efficacy. In some instances, a new non-medicinal ingredient may represent only quality concerns. For example, a reactive NMI with an established safety profile may impact on formulation stability and would require chemistry and manufacturing data only to support the use of the NMI. As per current practice, the TPP will take into consideration and offer flexibility if the NMI has been qualified in the quantity proposed and the route proposed in another jurisdiction with regulatory standards comparable to Canada. Similarly, the TPP will also take approved food uses into consideration.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

Complete the data elements of Sections I, II, III, IV and V.

Note: Sponsors should provide to the TPP the relevant documentation/data for NMI's that have been qualified in another regulatory jurisdiction

1.1.2.3 Category III Products: Subgroups and Data Elements

Sponsors must submit a Category III data package for a drug product when the Therapeutic Products Progamme has some prior experience or knowledge regarding the safety, efficacy and quality aspects of the active ingredient(s) in the drug product, but requires some additional data and information to facilitate a benefit-risk assessment.

The following are the Category III subgroups for drug products that contain an *active ingredient* previously licensed as a drug in Canada.

Subgroup III-1

The product contains an active ingredient that is judged essentially comparable to a biological substance previously licensed for sale as a drug in Canada, but which differs in the nature of the source material or manufacturing process. The product may not differ significantly in properties with regard to efficacy, although it may differ in respect to safety from that previously licensed biological substance. This subgroup intends to capture well characterisable biological products which will receive case-by-case consideration until there is international agreement on possible common standards.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

If the biological product submitted was previously licensed, some portions of the original submission may be valid for cross-referencing (Sections II, III, IV, V) perhaps with additional bridging studies appropriate to the situation. Data in the original submission should be re-analysed to determine areas of comparability between the two products. Table I should be used as a check list.

If the biological product submitted has not been licensed, but contains an "essentially comparable" active ingredient that was previously licensed, it is likely that a complete data package will be required in most cases. If sufficient comparative data are available to prove biocomparability with the previously licensed product, limited preclinical and clinical information (Section II, III and IV) may be accepted. An extended chemistry/manufacturing package (Section V) will usually be required to support the different source and

production processes.

Note: The Therapeutic Products Programme will require that the information available for a drug product under Subgroup III-1 be as comprehensive as that necessary to assess a new active substance in Category IV.

Subgroup III-2

The product contains an active ingredient that is a chemical or biological substance that has been previously licensed for sale in Canada and the product is presented for:

a)a change to or an extension of an existing indication that does *not* result in a change, in relation to the indication of the previously licensed product, at the third level of the Anatomical Therapeutic Chemical (ATC) classification code; or

b)a change to or an extension of the dosage regimen or an additional dosage regimen not previously licensed for a drug product containing that active ingredient in Canada.

Data Elements

Some information previously submitted to support the original drug product may be sufficient to allow a benefit-risk assessment of the new drug product. When comparing the original and new drug products, consider whether:

i)a new demographic group will be exposed to the active ingredient;
ii)the population will be exposed to lesser or greater amounts of the active ingredient; and
iii)the mode of action and pharmacology of the active ingredient are different.

Experts should conduct comparisons of the drug products and the implications of differences in each of the areas listed in the submission. Scientific justification must be used for all cross-references to previously submitted data in each of the data elements. Bridging studies may be necessary to demonstrate the validity of previously submitted data.

Note: For an explanation on use of ATC codes, see clarification note at end of Category IV-4 data requirements.

Subgroup III-3

The product contains an active ingredient that is a chemical or biological substance previously licensed for sale in Canada and the active ingredient is presented for a change in schedule status.

Data Elements

***Use*Section 1: Table 3--Factors Affecting Changes in Schedule F Status**

Table 3 outlines the ten factors and three exceptions to be considered in regard to the listing of substances on Schedule F to the *Food and Drug Regulations* which prohibits the sale of a drug to the general public without a prescription. These factors relate to the use, safety and effects of the drug product, and the disease treated by the drug product. In making a representation using Schedule F, all issues listed on Table 3 must

be addressed.

Subgroup III-4

The product contains an active ingredient that is a chemical or biological substance previously licensed for sale in Canada that is presented as:

a)a new route of administration;

b)a new dosage form;

c) a novel delivery system.

Data Elements

For this subgroup the data needs are often very specific to the individual drug product. It is the intention that this subgroup be highly flexible. It is recognized that in some cases, a new dosage form or route of administration represents no change in the quality, safety or efficacy profile and the necessary supporting data elements may be minimal. In other instances the modifications to the drug product may impart significant effects which will require comprehensive data elements to facilitate a risk/benefit decision.

The general data elements necessary for products in subgroup III-4 a, b or c are outlined individually below along with notes on areas of intended flexibility.

Subgroup III-4anew route of administration

Data Elements

***Use*Section 1: Table 4--Pre-market Data Elements for Subgroup III-4a: A new route of administration**

Generally, the development of a new route of administration for an existing drug product has been conducted within the framework of the original drug product. Therefore, it is likely that much of the information in the original submission is adequate to address some of the issues related to the new drug product.

There are approximately 50 routes of administration used for drug products sold in Canada. Therefore, there are many possible changes. The Therapeutic Products Programme has used the changes in routes of administration in the table below as examples to indicate, in Section 1: Table 4, possible areas of compatible data between existing and new drug products. Those areas of the submission that may be valid for cross-reference have been deleted from Table 4:

Note: The columns in Table 4 specify additional information required for the change in the route of administration indicated at the top of the column.

Original Route	Proposed Route
Oral	Injectable

Original Route	Proposed Route
Injectable	Oral
Oral or Injectable	Another route for systemic effect
Oral or Injectable	Another route for local effect

Subgroup III-4bnew dosage form

Data Elements

***Use*Section 1: Table 5--Pre-market Data Elements for Subgroup III-4b: An original oral product to a modified release product**

This subgroup is only for changes of dosage form. Other changes to the drug product, e.g., a concomitant change in route of administration, will require the submission of data specified under another subgroup.

This subgroup includes numerous possibilities of dosage forms. The Therapeutic Products Programme has used the examples in the table below to illustrate, in Section 1: Table 5, possible areas of compatible data between existing and new drug products.

In the first case - **tablet to capsule change**, comparative data to support the safety and effectiveness of the new drug product should demonstrate the relative clinical effectiveness, the relative pharmacodynamic performance or the bioequivalence of the two drug products.

Original Dosage Form	Proposed Dosage Form
Tablet	Capsule
Tablet, Capsule or Solution	Modified Release
Topical Solution	Topical Cream

However, the second case - **a drug product proposed for use as a modified release dosage form**, requires more extensive information. Sponsors must:

- provide bridging studies to ensure the validity of the original toxicology data under Section II;
- fulfil much of Section III to validate the new dosage form; and
- demonstrate the clinical effectiveness of the new product under Part IV.

In the third case - **topical solution to topical cream**, the example assumes that the drug product is intended for local effect. Sponsors:

- must demonstrate that the original toxicology is valid for the new drug product; dermal irritation and dermal sensitization studies may also be needed to support the new formulation
- may have to provide comparative studies measuring relative absorption of the drug products; and
- as the drug product is intended for local effect, sponsors must demonstrate efficacy by clinical data.

In all of the above cases, if the source of raw material used in the two drug products is identical, sponsors may cross-reference Section V, Part A, *Drug Substance* from the submission for that drug product. Given the nature of the new dosage form, additional information on the drug substances may be needed. For example, information on particle size or impurity limits may be warranted as a result of changing the dosage form.

Subgroup III-4cnovel delivery system

Data Elements

Use: **Section 1: Table 4-- Pre- market Data Elements for Subgroup III-4a and 4c**

Complete the data elements of section I, II, III, IV and V; disregard the last two columns on the page specific to a new route of administration.

Generally, the development of a novel delivery system for an existing drug product has been conducted within the framework of the original drug product. Therefore, it is likely that much of the information in the original submission is adequate to address some or many of the data requirements related to the new drug product and that only very specific studies need to be conducted. For example, an irritation study and sensitization study along with a comparative pharmacokinetic study which demonstrates similar systemic dosing from the original dosage form and from a novel topical dermal patch delivery system may be sufficient as a bridge to the safety and efficacy data base submitted on the original dosage form. Where appropriate, sponsors are encouraged to cross reference to the original submission to fulfil data requirements.

Subgroup III-5

The product contains an active ingredient that is a chemical substance listed on the Biopharmaceutics List[2], and is presented for systemic effect in one of the following dosage forms where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada:

a)a solid oral dosage form;
b)an oral suspension;
c)a powder or granules for oral suspension; or
d)an oral solution.

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[2] The Biopharmaceutics List will be developed and will encompass both bioavailability and pharmaceutical chemistry issues. For more information on this list, see Appendix 1.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

These data elements apply only to drug products for which a Canadian reference product is available.

Sponsors must demonstrate that the drug product is comparable in both its safety and efficacy to the reference product. Therefore, a submission of comparative data that focuses on the clinical or pharmacodynamic performance of the drug products or on the relative bioequivalence of the drug products may be sufficient.

Sponsors must also provide the drug product quality data in Section V.

Note: Sponsors should note that some products within this group may qualify for waiver of bioequivalence data based on definitive demonstration of pharmaceutical equivalence.

Subgroup III-6

The product contains an active ingredient that is a chemical substance listed on the Biopharmaceutics List that is contained in a combination with one or more other active ingredients where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada.

Data Elements - same as for III-5 above.

Subgroup III-7

The product contains an active ingredient that is a chemical substance presented as one of the following dosage forms where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada:

a)a modified release dosage form;
b)a solution for inhalation;
c)a suspension or powder for inhalation;
d)an injectable preparation, which may or may not be intended for use as a solution;
e)a peritoneal dialysis solution;
f)a hemodialysis solution;
g)an ophthalmic preparation;
h)a rectal suppository that delivers the active ingredient systemically through absorption;
i)a dermal topical, vaginal or nasal preparation intended for local effect;
j)an otic preparation; or
k) a dermal topical that delivers the active ingredient systemically through absorption

Data Elements

Specific data elements that should be submitted for products in each of the subgroups a-k are listed below.

Note: Sponsors should note that some products within this group may qualify for waiver of bioequivalence data based on definitive demonstration of pharmaceutical equivalence. However, comparative pharmacodynamic or clinical studies may be required to establish the relative safety and efficacy in relation to the reference product if pharmaceutical equivalence cannot be established.

Subgroup III-7amodified release dosage form

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

This subgroup is **only** for drug products for which there is a reference product on the market. First-time modified release products are subject to Subgroup III-4b.

Sponsors must demonstrate that the drug product is comparable in both its safety and efficacy to the reference product. Therefore, a submission of comparative data that focuses on the clinical or pharmacodynamic performance of the drug product or on the relative bioequivalence of the drug products may be sufficient.

If the sponsor has another drug product containing the same active ingredient that is already licensed, sponsors may cross-reference Section V, Part A, *Drug Substance* from the submission for that licensed drug product. Dependent on the nature of the dosage form, physico-chemical characteristics and methods of manufacturing of the drug products, additional drug substance information may be necessary.

Subgroup III -7bsolution for inhalation

Data Elements

Use	**Section 1: Table 6--Pre-market Data Elements for Subgroup III-7b: A solution for inhalation**

Sponsors must provide an adequate assessment of equivalence between their drug product and a product already on the market. It may be sufficient to submit *in vitro* test data only.

However, in the case of a drug product for which the sponsor cannot generate this data or show that the formulation is the same as the reference product, pharmacodynamic or clinical data must be submitted.

Subgroup III-7csuspension or powder for inhalation

Data Elements

***Use*Section 1: Table 7--Pre-market Data Elements for Subgroup III-7c: A suspension of powder for inhalation**

Currently, there is not an adequate link between *in vitro* performance of these drug products and their clinical safety and efficacy. The sponsor must compare the proposed and reference product's formulation and *in vitro* characteristics and provide clinical data.

Subgroup III-7dinjectable preparation, may or may not be intended for use as a solution

Data Elements

***Use*Section 1: Table 8--Pre-market Data Elements for Subgroup III-7d: An injectable intended to be used as a solution** ***or*Section 1: Table 9--Pre-market Data Elements for Subgroups III-7d and III-7h: An injectable not to be used as a solution and a rectal suppository that delivers the drug systemically**

The Therapeutic Products Programme decided that the final physical properties of proposed drug products determines their subgroup. If the drug product is to be used as a solution it must fulfil the requirements set out in Table 8. This applies whether the product will be sold as a solution or powder for solution.

However, if the drug product will not be administered as a solution, but rather in another physical form, e.g., as a suspension, it must fulfil the requirements set out in Table 9.

Subgroup III-7eperitoneal dialysis solution

Data Elements

***Use*Section 1: Table 10--Pre-market Data Elements for Subgroup III-7e: Peritoneal dialysis solutions**

Subgroup III-7fhemodialysis solution

Data Elements

***Use*Section 1: Table 11--Pre-market Data Elements for Subgroup III-7f: Hemodialysis solutions**

Subgroup III-7gophthalmic preparation

Data Elements

*Use*Section 1: Table 12--Pre-market Data Elements for Subgroup III-7g: An ophthalmic preparation

Subgroup III-7hrectal suppository that delivers active ingredient systemically

Data Elements

*Use*Section 1: Table 9--Pre-market Data Elements for Subgroups III-7d and III-7h: Injectables not used as solutions and a rectal suppository that delivers the drug systemically

Subgroups III-7idermal topical, vaginal or nasal preparation intended for local effect III-7jotic preparation

Data Elements

*Use*Section 1: Table 13--Pre-market Data Elements for Subgroups III-7i and III-7j: Dermal topical, vaginal or nasal preparations for local effect and an otic preparation

Subgroup III-7kdermal topical intended for systemic effects

Data Elements

*Use*Section 1: Table --Pre-market Data Elements for Subgroups IIIk: A dermal topical that delivers the drug systemically

Sponsors may provide an adequate assessment of equivalence between their drug product and a product already on the market, in addition to irritation and sensitization studies.

In the case of a drug product where the sponsor cannot generate adequate comparative data, pharmacodynamic or clinical data may be required.

Group III-8

The product contains a pharmaceutical active ingredient that is a plant or of plant origin previously licensed for sale in Canada and not marketed within the scope of the *Therapeutic Products Directorate Guidelines: Traditional Herbal Medicines*.

Data Elements

Use	**Section 1: Table 1--General Pre-market Data Elements**

The data elements to support the safety and efficacy of these products are equivalent to those specified under Subgroups III-5 and III-6.

If relative bioequivalence of the proposed and currently licensed products cannot be established, relative pharmacodynamic performance or clinical efficacy must be demonstrated.

Part V must include, in addition to a complete data package, adequate botanical characterization and test procedures to ensure that the quality of the drug product does not differ from that of the licensed product.

1.1.2.4Category II Products: Subgroups and Data Elements

Sponsors must submit a Category II data package for a drug product for which there is extensive prior experience or knowledge regarding the safety, efficacy and quality aspects of the active ingredient(s). The Therapeutic Products Programme will make decisions on product safety and efficacy based on precedents in the marketplace. For numerous drug classes in this category, labelling standards currently exist. It is the intention of the Therapeutic Products Programme to develop labelling standards where applicable, for additional drugs within this category thereby reducing the requirement for data submission. Sponsor attestation of compliance with a developed labelling standard would then constitute the data submission. In the interim and when labelling standards do not exist, limited data and information submission will continue to be required as outlined below.

The following are the Category II subgroups for drug products that contain an *active ingredient* previously licensed as a drug in Canada.

Subgroup II-1

The product contains an active ingredient that is a chemical or biological substance previously licensed for sale in Canada and the product is presented for:

a)a new indication;

b)a change to or an extension of an existing indication; or

c)a change to, an extension of or an additional dosage regimen, **and** where that indication or dosage regimen has been previously licensed for that active ingredient in Canada.

Data Elements

Use	**Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Form A.

Subgroup II-2

The product contains an active ingredient that is a chemical or biological substance *not* listed on the Biopharmaceutics List and is presented for systemic effect in one of the following dosage forms where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada:
a) a solid oral dosage form;
b)an oral suspension;
c)a powder or granules for oral suspension;
d)an oral solution.

Data Elements

***Use*Section 1: Table 1--General Pre-market Data Elements** ***and*Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Table 1, Section V. *It should be noted that the specific data elements from Section V that would be necessary to support the submissions for this subgroup are currently under development in the TPP. Until finalized, some elements from Table 1, Section V may apply.*

Complete Form A.

Subgroup II-3

The product contains an active ingredient that is a chemical or biological substance *not* listed on the Biopharmaceutics List that is contained in a combination with one or more other active ingredients where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada.

Data Elements

***Use*Section 1: Table 1--General Pre-market Data Elements** ***and*Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Table 1, Section V. *It should be noted that the specific data elements from Section V that would be necessary to support the submissions for this subgroup are currently under development in the TPP. Until finalized, some elements from Table 1, Section V may apply.*

Complete Form A.

Subgroup II-4
The product contains an active ingredient that is a chemical or biological substance presented as:

Subgroup II-4aophthalmic preparation intended for one of the following uses where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada:

i) artificial tears;
ii) an eye wash; or
iii) a contact lens solution;

Data Elements

***Use*Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Form A.

Provide specifications with limits and a description of the analytical methods for the **active ingredients** with reference to pharmacopoeial methods where possible.

Provide specifications with limits and a description of the analytical methods for the **finished drug product** with reference to pharmacopoeial methods where possible.

Provide the manufacturing instructions and/or master formula to be used to manufacture the drug product. These should include all steps to ensure the sterility and apyrogenicity of the product including all in-process controls.

Provide a certificate of analysis for one lot of the finished drug product.

Provide the name and address of the fabricator and importer if applicable.

Subgroup II-4brectal suppository that delivers the active ingredient systemically through absorption, where a Labelling Standard exists;

Data Elements

***Use*Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Form A.

Provide specifications with limits and a description of the analytical methods for the **active ingredients** with reference to pharmacopoeial methods where possible.

Provide specifications with limits and a description of the analytical methods for the **finished drug product** with reference to pharmacopoeial methods where possible.

Provide a certificate of analysis for one lot of the finished drug product.

Provide the name and address of the fabricator and importer if applicable.

Subgroup II-4cdermal topical, vaginal or nasal preparation intended for local effect, where a Labelling Standard exists

Data Elements

***Use*Section 1: Form A--General Information Section of the Drug Submission Application** ***or*Section 1: Table 13--Pre-market Data Requirements for Subgroups III-7i and III-7j: Dermal topical, vaginal or nasal preparations for local effect and an otic preparation**

When the formulation does not contain non-medicinal ingredients that affect the absorption of the active ingredient, complete Form A in addition to the information specified in the appropriate monograph.

However, if the above situation does not apply, fulfil requirements for Subgroup III-7i.

Subgroup II-4dotic preparation, where a Labelling Standard exists

Data Elements

***Use*Section 1: Form A--General Information Section of the Drug Submission Application**

Complete Form A and the information specified in the appropriate monograph.

Subgroup II-5

The product contains an active ingredient that is represented for use as a hard surface disinfectant.

Data Elements

Use*Therapeutic Products Directorate Guidelines: Disinfectant Drugs* (Cat. No. H42-2/61-1994)

Subgroup II-6

The product contains an active ingredient that is a plant or of plant origin and intended to be marketed within the scope of the *Therapeutic Products Directorate Guidelines: Traditional Herbal Medicines*.

Data Elements

UseTherapeutic Products Directorate Guidelines: Traditional Herbal Medicines (Cat. No. H42-2-36-1990)

Subgroup II-7

The product contains an active ingredient that is intended to be marketed as a Homeopathic Medicine within the scope of the *Therapeutic Products Directorate Guidelines: Homeopathic Preparations: Application For Drug Identification Numbers.*

Data Elements

UseTherapeutic Products Directorate Guidelines: Homeopathic Preparations: Application For Drug Identification Numbers (Cat. No. 42-2-21-1990)

Subgroup II-8

The product is a commercial radiopharmaceutical prepared from approved kits. For example, a Tc-99m medronate injection prepared from medronate kit and dispensed into vials or unit dose syringes would be classified to this subgroup.

Data Elements

Stability data if dispensed into vials or unit-dose syringes

Information on vials and syringes used

1.1.2.5 Category I Products: Criteria and Monographs

Drug products in Category I present minimal risks. Extensive prior knowledge and experience regarding the safety, efficacy and quality aspects of the active ingredient(s) are available. Data and information submission requirements may be satisfied by a sponsor's attestation against a public standard. A drug product must meet **all of the following criteria** to fit this category:

- The drug product is indicated for the prevention or relief of minor self-limiting conditions or their symptoms;
- The intended use will not delay recognition of serious ailments;
- The drug product has not been associated with clinically significant and/or a high incidence of adverse effects;

- The drug product contains only therapeutically rational ingredients and no medicinal ingredient superfluous to the treatment for which it is intended;
- The drug product has no significant potential for accidental poisoning or misuse. Misuse should not result in a significant health hazard;
- Directions for use are simple, uncomplicated and easy to follow;
- Cautionary statements, if required, are minor in nature and scope; and
- Appropriate selection and use of the drug product do not require the intervention of a health professional.

Category I Monographs

The following 13 monographs are available on Category I products:

Monographs	Latest Revision
Acne Therapy	January 10, 1995
Antidandruff Products	January 9, 1995
Antiperspirants	January 9, 1995
Antiseptic Skin Cleansers	December 20, 1994
Athletes Foot Treatments	January 11, 1995
Contact Lens Disinfectants	January 11, 1995
Fluoride Containing Anti-caries Products	January 10, 1995
Hard Surface Disinfectants	January 13, 1995
Medicated Skin Care Products	December 7, 1994
Mineral Supplements	January 10, 1995
Sunburn Protectants	January 9, 1995
Throat Lozenges	January 13, 1995
Vitamin Supplements	December 19, 1994

Data Elements

Sponsor attestation to conformance with a Class Monograph.

1.2Licensing and Assignment of Reporting Schedule

1.2Licensing and Assignment of Reporting Schedule

1.2.1General Overview

A general overview of the licensing process and assignment of post-approval reporting schedules is presented in this section. However, for specific details on product licence reporting schedules and requirements and the periodic product reassessment, please refer to Section 2, Post-Approval, of this document.

At the conclusion of the pre-market review, a favourable benefit/risk ratio and acceptable quality review will facilitate the issuance of a licence to market the drug product. Upon licensing, the drug product will also receive one of three (type A, B or C) reporting schedules which in turn will dictate the reporting requirements that must be fulfilled while the drug is being marketed. The reporting schedules are differentiated on the basis of potential risk posed by the drug product as defined by the level of concern and uncertainty about the safety of the drug product in the marketplace and on the potential or actual risks identified about the product during the review process. Within this scheme, a new active substance for which there is no available data on safety in the market place will have a higher level of concern and uncertainty and may receive a licence to market with schedule A reporting requirements. Schedule A reporting will ensure that the product receives close scrutiny for safety during the first three years on the Canadian market. Similarly, a drug product with a hepatotoxicity concern identified during the review process but for which the benefit/risk warrants market authorization, may also be licensed with schedule A reporting requirements to ensure a high level of scrutiny. At specified times, as experience is gained on the safety of the product in the market place, periodic reassessment of the product and reporting requirements will occur. A favourable review will allow a reduction in level of post approval safety reporting and scrutiny. When the drug product has sufficient market safety experience and has demonstrated that safety concerns can be effectively managed, or when there are minimal safety issues, the product will receive a reporting schedule with minimal post-approval requirements.

Sponsors should note that the approach summarized above is consistent with regulatory approaches in the U.S. and Europe. For companies with international interest, it is intended that reporting schedules described in the PLF will facilitate the submission of a singular report simultaneously to various regulatory jurisdictions.

The criteria that were developed to facilitate assignment of all drug products into the three reporting schedules are outlined below.

1.2.2Criteria for Assignment of Post Approval Reporting Schedules

1.2.2.1Schedule A Reporting

A drug product will be assigned schedule A reporting requirements if it meets one or more of the criteria listed below. Some drugs which meet the criteria may be exempt from schedule A reporting provided they have demonstrated a substantial post-approval record of quality, efficacy and safety.

1.A drug product that is a new active substance (NAS) including:

i) a combination involving a NAS

ii) a biological substance previously licenced for sale as a drug in Canada which differs in molecular structure, nature of source material or a significant change in manufacturing process that impacts on safety and efficacy, or differing in properties with regard to safety and efficacy from that previously licenced biological substance

Note: for radiopharmaceuticals, a NAS also means a new combination of carrier molecule and radionuclide

2.A drug product with a narrow therapeutic range where deviation has serious consequence with respect to toxicity or lack of efficacy

3.A drug product with high potential for serious toxicological risk, demonstrated serious toxicological risk or post-approval evidence from other countries of serious toxicity including important drug-drug interactions, unexpected or unexplained deaths where the risk profile warrants ongoing monitoring or where the risk needs to be more closely assessed to facilitate better management strategies.

4. A drug product authorized for:

i) a major new prescription indication comparable to the first, second or third level of the Anatomical Therapeutic Chemical (ATC) classification code

(see note under Category IV-4 for details on use of ATC classification code for determination of change in indication),

ii) a new patient population e.g. pediatric use when previous indication and use was in adults

5.A drug product with a novel delivery system where there is a high uncertainty factor regarding safe use or efficacy e.g. dermal implants for hormonal therapy.

6.A drug product with new conditions of use where there is a high uncertainty factor regarding safe use or efficacy e.g. metered dose inhalers utilizing new nozzle technologies

7.A drug product indicated for a rare disease or with likelihood of low utilization/exposure rates where additional clinical information is necessary

8.A drug product containing new excipients with a high uncertainty factor regarding safe use e.g. metered dose inhaler incorporating a novel propellant

9.A drug product with potential for abuse e.g. the drug has a structure-activity relationship to known drugs of abuse or where the a change in the utilization profile in the market place indicates potential abuse.

Note: for the purposes of the PLF, uncertainty factor refers to the level of knowledge and concern regarding:
a) extent, quality and limitations of animal data to predict human safety, and
b) extent, quality and limitations of pre and post-approval human experience with the drug product to enusre exposure in a heterogeneous human population.

1.2.2.2Schedule B Reporting
Drug products will automatically receive schedule B reporting requirement if they do not meet the criteria set for either schedules A or C.

In addition, a drug product which has received authorization for a switch from prescription to non-prescription status will also be considered for schedule B reporting.

1.2.2.3Schedule C Reporting
A drug product will be considered for schedule C reporting provided it has no known biopharmaceutical concern, low risk potential for development of dependence or resistance and contains only established, well recognized and accepted excipients at recognized safe levels. In addition, the product should meet any one of the following criteria:

1.A drug product for which a Category I Class Monograph has been developed.

2.A drug product with an established (has completed schedule B reporting) marketing history of dosage form, route of administration and indication/condition for use*, with no history of identified safety concerns and no serious unexpected or unexplained adverse drugreactions. Sponsors wishing to have their product considered for schedule C according to this criteria item, must review and analyse world-wide data on the drug substance at the time of application, attest that the analysis demonstrated no issues of concern and the analysis must be available on request from the Therapeutic Products Programme.

A waiver for this requirement for data analysis will be granted to drug products with a Category I Class Monograph.

**A drug product receiving authorization for switch from prescription to non-prescription status will be considered as a new condition of use and will not be eligible for schedule C reporting.*

3.A drug product with a well defined risk profile for which the risks can be appropriately managed through labelling or other reasonable controlling measures.

1.2.3Change in Reporting Schedule

1.2.3.1Movement to a Less Frequent Reporting Schedule

The movement of products from schedule A to B or B to C reporting requirements will occur by default after the reporting period is completed. Scientific rationale will be needed to justify the retention of a product in a particular schedule once the reporting cycle is complete. Although time in the marketplace is considered the prime determinant for the time period for post-approval reporting, there may be instances when there is sufficient and acceptable data on exposure which may be taken into consideration by the Programme. Sponsors should also note the timeframe specified for reporting on a particular drug product may not be adequate to gather sufficient safety information on a product with very limited exposure. In such instances, a particular reporting schedule may need to be extended to establish the post-approval safety profile.

1.2.3.2Movement to a More Frequent Reporting Schedule

When warranted, products may be moved from a lower post-approval reporting schedule into a higher reporting schedule. Some preliminary criteria that would support such a movement have been developed.

A drug product will be considered for increase in reporting requirements under the conditions outlined below:

1.Receipt of information or adverse drug reaction reports which qualify the product for schedule A reporting

2.Receipt of spontaneous adverse drug reaction reports that cannot be easily accommodated through labelling

3.Warning signals that there is a need to generate more safety information which requires more stringent reporting

4.A drug product that undergoes switch from prescription to non-prescription status and Canada is the first country where the switch occurs

5.A drug product presented for a major new indication

1.2.4New Drug Products

A new drug product will fit into one pre-market category and subgroup and the drug submission application must contain the required data and information outlined for that category and subgroup. At the conclusion of the pre-market evaluation, the Therapeutic Products Programme will decide whether the submitted data and information are sufficient to establish quality, safety and efficacy and whether conditions of labelling and sale provide a favourable benefit-risk balance. If the decision is positive, the Therapeutic Products Programme will licence the product for sale and assign the post-approval reporting schedule (A, B or C). The reporting schedule will determine the post-approval monitoring schedule and the types of reports that need to be prepared and submitted to the Programme or kept on site.

1.2.5Previously Licensed Drug Products

Sponsors of drug products with changes other than those subject only to notification must file a licence amendment application containing the data and information specified within the pre-market category/subgroup applicable to the change. For example, if a sponsor applies for a major new indication for a drug product, the submission requirements of Category IV- 4 apply and the sponsor will need to submit the data necessary to support the change. The Programme will review the reporting schedule prior to issuing a new product licence. Dependent on the nature of the change to the product, post-market reporting requirements could increase, decrease or remain the same as the original reporting schedule. Sponsors can market a drug product under one reporting schedule only. New regulations will give the Therapeutic Products Programme the authority to cancel a previous licence with a specific reporting schedule once a new licence with a new reporting schedule is issued for a product.

1.2.6Existing (Marketed) Drug Products

On the date that the new licensing system is put in place, the Therapeutic Products Programme will issue a licence and reporting schedule for all marketed drug products based on the criteria developed for schedule A, B or C reporting. A product which meets the criteria outlined for schedule A will need to fulfil the post-approval reporting requirements according to the specifics outlined in Section 2, Table 1. All marketed products which meet the criteria outlined for schedule C reporting will be designated to that group. By default, all other drug products will receive schedule B reporting requirements. Drugs which have received authorization for a switch from prescription to non-prescription status during the previous 3 years will receive schedule B reporting requirements.

Although all marketed drug products will be assigned to one of the three reporting schedules when the PLF is implemented, sponsors will prepare safety reports **prospectively** from the time

of implementation. The exception is for products wishing to be considered under item 2 of Schedule C Reporting. For such products, sponsors must conduct a general review and analyse world-wide data on the drug substance at the time of application to ensure the safety of the product (for specific details, see Section 1.2.2.3, Schedule C Reporting).

1.2.7Conditional Licence

The Therapeutic Products Programme may issue a conditional licence (CL) for a drug product that is subject to Category IV pre-market requirements **and also** meets the requirements of the Policy on Priority Review. The following factors apply to conditional licences:

- Data development requirements will be assigned upon issuance of the CL. Sponsors will have to submit post-marketing confirmatory studies to demonstrate that the product considered for the conditional license has a clinical benefit, on the basis of surrogate markers or early trial results;

- The length of time for the conditional licence will be negotiated at the time of conditional approval. License holders must understand that a conditional licence comes with a **presumption of non-renewal**;

- The Therapeutic Products Programme may cancel the licence if safety concerns arise on the basis of the confirmatory studies and information collected and reported during the conditional period; and

- A conditional licence is the first step towards a licence if confirmatory studies demonstrate that a drug approved initially on surrogate markers or early trial results has the required clinical benefit.

1.3SECTION 1: TABLES AND FORMS

1.3SECTION 1: TABLES AND FORMS

This part of the document contains the tables and forms for Section 1 which described the pre-market data elements for the drug categories and subgroups. There are 14 tables and one form. Tables 1-14 come first and FORM A (HPB 3011 3-91) is last.

When using the tables and forms, the following should be kept in mind:

- **Section 1: Table 1--General Pre-market Data Elements** outlines the comprehensive pre-market data package. It is the basis for all the other tables except Table 3.

- To avoid repetition, subsequent tables may list the title of a section but not the subheadings listed on Table I. When subheadings are noted on a subsequent table, sponsors must refer to Table 1 and fulfil all the elements of that section. For example, if Section I, *General Data Elements*, is listed without subheadings, sponsors must refer to Table 1, Section I and submit all the information listed in its sub-headings: *Foreign Status, Canadian Status* and *Proposed Labelling*. Therefore, in many cases, sponsors will use both the subgroup table and Table 1.

It is important to remember that the data elements attached to each subgroup apply to that subgroup only. When more than one subgroup applies to a drug product, then the data elements for each applicable subgroup must be fulfilled.

It is also important to note that the list of data elements are intended to be flexible. The general data elements tabulated for each category are necessarily at the highest common level to ensure that the Programme can obtain the comprehensive data submission essential for decision making. For example, Table I lists all of the pre-market data that are recognized internationally as necessary for a risk/benefit decision for a new active (pharmaceutical) substance. However, it is recognized that some of the pre-clinical safety studies listed on that table may not be applicable to a new biological product and as such would not constitute part of the core pre-market data submission for such products. Sponsors should use the tables as guides for the necessary data elements for their specific product.

SECTION 1: TABLE 1
GENERAL PRE-MARKET DATA ELEMENTS

I GENERAL DATA ELEMENTS	
A. **FOREIGN STATUS**	
1. Countries where the drug is marketed	
a. Indications/route of administration/number of years marketed	
2. Countries where the drug was submitted for approval	
a. Date of filing and status	
i) pending	
ii) withdrawn	
iii) refused	
b. Reasons and dates where applicable	
3. Countries where the prescribing information (labelling) was changed after approval	
a. Dates and reasons for changes	
4. Package inserts from all countries where the drug has been approved	
5. List of completed and in-progress studies	
B. **CANADIAN STATUS**	
1. List of prior related submissions	
a. INDs (by objectives and/or indications)	
b. Completed studies	
c. In-progress studies (i.e. for other indications)	
i) studies included in the submission	
ii) other studies	
2. Other related submissions: NDS, S/NDS, Master Files, etc.	
3. Emergency Drug Release summary	
C. **PROPOSED LABELLING**	
1. Product Monograph	
2. Package Insert	

3. Draft Labels	
II IN VITRO AND ANIMAL STUDIES	
A. **PHARMACOLOGY**	
1. General Pharmacology	
a. In-Vitro Studies	
i) receptor binding assays	
ii) levels and turnovers of neurotransmitters and their metabolites	
iii) biochemical pathways to determine potential mechanism of action	
b. In-Vivo Studies	
i) actions related to predicted therapeutic activity, secondary activity	
ii) actions related to safety	
iii) results of broad screening	
2. Other Effects	
a. Tolerance/ Tachyphylaxis/ Supersensitivity	
b. Rebound/Withdrawal Effect	
c. Dependence Liability (where applicable)	
B. **PHARMACOKINETICS/TOXICOKINETICS**	
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)	
a. Drug distribution	
b. Tissue/fluid levels	
c. Blood/brain barrier	
d. Placental/milk transfers	
e. Effect of route of administration on ADME	
2. Comparative Pharmacokinetics/ toxicokinetics	
a. Interspecies	
b. Animal vs human	
c. Comparative ADME (animal vs human)	
3. Enzyme Induction/ Inhibition	

4. Microsomal Isozyme(s)	
5. Other	
C. **TOXICOLOGY**[3]	
1. Single dose toxicity (acute toxicity)	
2. Multiple dose toxicity (subchronic, chronic toxicity)	
3. Carcinogenicity	
4. Mutagenicity	
5. Reproduction/Teratology (may include neurotoxicity in special cases)	
6. Special studies when applicable	
a. Neurotoxicity	
b. Hepatotoxicity	
c. Nephrotoxicity	
d. Immunotoxicity	
e. Irritation	
f. Antigenicity	
g. Phototoxicity	
h. Photocarcinogenicity	
i. Joint toxicity	
j. Old vs young animals	
k. Ototoxicity	
l. Special studies	
m. Other studies	
7. Environmental impact studies - where necessary to meet requirements under other relevant legislation	
a. Handling of drug	
b. Disposal of drug	
c. Manufacturing process(es)	

[3] *Toxicological Evaluation*, Cat. No. H42-2-15-1990

D. **MICROBIOLOGY**	
1. Sensitivity - clinical and laboratory	
a. Static	
b. Cidal	
c. Effects on activity	
i) inoculum	
ii) culture media	
iii) biological fluids	
iv) pH	
2. Mechanism of action	
3. Mechanism of resistance	
4. Post-antibiotic effect	
5. Interaction with other antibiotics	
6. Susceptibility test methods	
7. In-vivo animal models	
8. Metabolism by organisms	
9. Other (as applicable)	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
1. Pharmacokinetics	
a. Absorption/ distribution/ metabolism/ excretion (ADME)	
i) drug distribution	
ii) tissue/fluid levels	
iii) blood/brain barrier	
iv) placental/milk transfer	
v) effect of route of administration on ADME	
b. Comparative pharmacokinetics (animal vs human)	
c. Enzyme induction/ inhibition	
d. Microsomal isozyme(s)	

e. Population kinetics	
f. Kinetics regarding age/ gender/ race	
g. Kinetics in organ impaired (renal, hepatic) patients	
h. Disease/drug interaction studies	
i. Drug/drug interaction studies	
j. Food/drug interaction studies	
k. Special studies	
i. Other studies (i.e. where applicable, dosimetry calculations for radiopharmaceuticals)	
2. Pharmacodynamics	
a. Single dose tolerance studies	
b. Multiple dose tolerance studies	
c. Disease/drug interaction	
d. Drug/drug interaction	
e. Food/drug interaction	
f. Special population studies[4]	
g. Other studies	
3. Bioavailability[5,6,7]	
IV CLINICAL STUDIES[8]	
A. DOSE RANGING STUDIES[9]	

[4] *ICH - Studies in Support of Special Populations: Geriatrics*, Cat. No. H42-2/67-1-1994

[5] *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A*, Cat. No. H42-2-/56-1992

[6] *Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B*, Cat. No.H42-2/56-1-1993

[7] Draft Report - *Bioavailability of Oral Dosage Formulations of Drugs Used for Systemic Effects, Report C.* HPB, Dec. 1992.

[8] *Conduct of Clinical Investigations*, Cat. No H42-2-14-1989

[9] *ICH - Dose Response Information to Support Drug Registration*, Cat. No. H42-2/67-4-1994

B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
b. Open studies	
c. Other studies (if applicable) - irritation, sensitization	
2. Long term studies	
a. Efficacy studies	
i) Controlled studies	
ii) Open studies	
b. Safety studies	
i) Controlled studies	
ii) Open studies	
c. Other studies (if applicable)	
C. SPECIAL STUDIES (Related to disease and/or concomitant therapies)	
D. ON-GOING STUDIES (Progress report on safety (ADR, dropouts, etc.)	
E. OTHER STUDIES	
1. Gender/age/race specific studies	
2. Realistic "quality of life" studies consistent with currently accepted standards for therapeutic class i.e. oncology drugs or drugs for treatment of HIV	
F. DOSIMETRY - where applicable, dosimetry calculations required for radiopharmaceutical products. .	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS [10,11]	
A. DRUG SUBSTANCE	
1. Pharmacopeial/ Reference Text Status	
2. Structural Relationship to Other Drugs of Similar Structure	

[10] *Chemistry and Manufacturing: New Drugs*, Cat. No. H42-2-30-1990

[11] As specified in Division of Information in, *Policy Issues: A Comprehensive Summary of Chemistry and manufacturing Information and a Certified Product Information Document*. The numerical designations of the divisions have been changed to be consistent with this document.

	3. Nomenclature	
	4. Source	
	5. Method of Manufacture	
	6. Development Chemistry	
	7. Impurities	
	8. Reference Standard	
	9. Control Tests on the Drug Substance	
	10. Batch Analyses	
	11. Packaging	
	12. Stability[12]	
B.	**DRUG PRODUCT**	
	1. Pharmacopeial Status	
	2. Production Site	
	3. GMP Status	
	4. Developmental Pharmaceutics	
	5. Formulation and Method of Manufacture	
	6. Excipients	
	7. Control Tests on the Finished Drug Product	
	8. Batch Analyses	
	9. Primary Packaging	
	10. Stability[11]	

[12] *ICH - Stability Testing of New Drug Substances and Products*, Cat. No. H42-2/67-3-1994

SECTION 1: TABLE 2
PRE-MARKET DATA ELEMENTS FOR SUBGROUP IV-5
A new combination of active ingredients

I GENERAL DATA ELEMENTS	
II IN VITRO AND ANIMAL STUDIES	
III HUMAN STUDIES	
IV CLINICAL STUDIES	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	
A. DRUG SUBSTANCE	
1. Pharmacopeial/ Reference Text Status	
2. Structural Relationship to Other Drugs of Similar Structure	
3. Nomenclature	
4. Source	
5. Method of Manufacture	
6. Development Chemistry	
7. Impurities	
8. Reference Standard	
9. Control Tests on the Drug Substance	
10. Batch Analyses	
11. Packaging	
12. Stability	
B. **DRUG PRODUCT**	
1. Pharmacopeial Status	
2. Production Site	
3. GMP Status	
4. Developmental Pharmaceutics	
5. Formulation and Method of Manufacture	
6. Excipients	
7. Control Tests on the Finished Drug Product	

8. Batch Analyses	
9. Primary Packaging	
10. Stability	

SECTION 1: TABLE 3
FACTORS AFFECTING CHANGES IN SCHEDULE F STATUS

Schedule F to the Food and Drug Regulations is a listing of chemical entities or classes of drugs which, with exceptions, are required by regulation to be sold by prescription.

Factors used to determine whether this level of control over the sale of these drugs is appropriate
1. They require individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring.
2. There exists a narrow margin of safety between the therapeutic and toxic dosages, especially in populations such as geriatrics, children and pregnant/nursing mothers.
3. They possess the potential or are known to cause undesirable or severe side effects at normal therapeutic dosage levels.
4. They are known by experimental data to induce toxicity in animals but have not been in clinical use for a sufficient period of time to establish the pattern or the frequency of long-term toxic effects in humans.
5. They are indicated for serious disease states often misdiagnosed by the public.
6. Their use may mask other ailments.
7. They have contributed to or are likely to contribute to the development of resistant strains of micro-organisms in humans.
8. They possess a sufficient dependence or abuse potential that has led or is likely to lead to harmful non-medical use if distribution is not supervised.
9. They possess a potentially high level of risk relative to their expected benefits.
10. They have a therapeutic effect based on recently elucidated pharmacologic concepts, the consequences of which have not been adequately established.
Exceptions
1. Drugs which are required to be readily available under emergency circumstances where it is not practical to obtain a prescription (such as adrenalin in insect-bite kits).
2. Drugs which are rarely used without a practitioner's supervision, and where the need for free availability outweighs the need for protection under Schedule F (such as insulin and nitroglycerin).
3. Drugs which have the potential to produce dangerous interactions with other drugs or food constituents but effective labelling can minimize this risk.

SECTION 1: TABLE 4
PRE-MARKET DATA ELEMENTS FOR SUBGROUPS III-4a and 4c
A new route of administration/novel delivery system

	Oral - Injectable Injectable - Oral	Oral / Injectable to another for systemic or local use
I GENERAL DATA ELEMENTS		
II IN VITRO AND ANIMAL STUDIES		
A. **PHARMACOLOGY**		
1. General Pharmacology		
b. In-Vivo Studies		
i) actions related to predicted therapeutic activity		
ii) actions related to safety		
B. **PHARMACOKINETICS/TOXICOKINETICS**		
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)		
e. Effect of route of administration/novel delivery system on ADME		
2. Comparative Pharmacokinetics/ toxicokinetics		
c. Comparative ADME (animal vs human)		
C. **TOXICOLOGY**		
2. Multiple dose toxicity (subchronic, chronic toxicity)		
5. Reproduction/Teratology (may include neurotoxicity in special cases)		
6. Special studies - i.e. irritation studies, sensitization	Local toxicity for injectables	Local toxicity for local use products
7. Environmental impact studies		
III HUMAN STUDIES		

A. **CLINICAL PHARMACOLOGY**		
1. Pharmacokinetics		
a. Absorption/ distribution/ metabolism/ excretion (ADME)		
i) effect of route of administration/novel delivery system on ADME		
b. Comparative pharmacokinetics (animal vs human)		
g. Kinetics in organ impaired (renal, hepatic) patients		
i. Drug/drug interaction studies		
j. Food/drug interaction studies	Only for products for oral administration	
2. Pharmacodynamics		
a. Single dose tolerance studies		
b. Multiple dose tolerance studies		
e. Food/drug interaction	Only for products for oral administration	
IV CLINICAL STUDIES		
A. DOSE RANGING STUDIES		
B. MAJOR STUDIES		
1. Short term studies		
a. Controlled studies		
b. Open studies		
c. Other studies (where applicable) i.e. irritation, sensitization		
2. Long term studies		
a. Efficacy studies		
i) Controlled studies		

ii) Open studies		
b. Safety studies		
i) Controlled studies		
ii) Open studies		
c. Other studies (if applicable)		
C. SPECIAL STUDIES (Related to disease and/or concomitant therapies)		
D. ON-GOING STUDIES (Progress report on safety (ADR, dropouts, etc.)		
E. OTHER STUDIES		
1. Gender/age/race specific studies		
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS		
A. DRUG SUBSTANCE		
B. DRUG PRODUCT		

SECTION 1: TABLE 5
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-4b
An original oral product to a modified release product

I GENERAL DATA ELEMENTS	
II IN VITRO AND ANIMAL STUDIES	
A. **PHARMACOLOGY**	
1. General Pharmacology	
b. In-Vivo Studies	
i) actions related to predicted therapeutic activity	
ii) actions related to safety	
B. **PHARMACOKINETICS/TOXICOKINETICS**	
1. Absorption/ Distribution/ Metabolism/ Excretion (ADME)	
a. Drug distribution	
b. Tissue/fluid levels	
e. Effect of route of administration on ADME	
C. **TOXICOLOGY**	
7. Environmental impact studies	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
1. Pharmacokinetics	
a. Absorption/ distribution/ metabolism/ excretion (ADME)	
i) drug distribution	
ii) tissue/fluid levels	
v) effect of route of administration on ADME	
b. Comparative pharmacokinetics (animal vs human)	
g. Kinetics in organ impaired (renal, hepatic) patients	
h. Disease/drug interaction studies	

i. Drug/drug interaction	
j. Food/drug interaction	
2. Pharmacodynamics	
a. Single dose tolerance studies	
b. Multiple dose tolerance studies	
c. Disease/drug interaction	
d. Drug/drug interaction	
e. Food/drug interaction	
f. Special population studies	
g. Other studies	
IV CLINICAL STUDIES	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	
A. DRUG SUBSTANCE[13]	
B. DRUG PRODUCT	

[13]If the drug substance is identical to the material used another product this information may be cross-referenced.

SECTION 1: TABLE 6
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7b
A solution for inhalation

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics[14]	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	
A. DRUG SUBSTANCE	
B. DRUG PRODUCT[15]	

[14]Pharmacodynamic or clinical studies may be required where comparative physical and *in vitro* testing are inadequate to demonstrate the safety and efficacy of the product.

[15]In addition to this data, product specific tests comparing the applicant' s product to the Canadian reference product should be submitted including:

a) comparative chemical analysis to demonstrate equivalent qualitative and quantitative composition (relying in part, on published information on the reference product - e.g. product monograph, labels, CPS) and,

b) comparative physico-chemical tests including osmolality, surface tension, droplet size (using lase diffraction, Cascade impactor or multi-stage impinger).

SECTION 1: TABLE 7
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7c
A suspension of powder for inhalation

I GENERAL DATA ELEMENTS	
IV CLINICAL STUDIES[16]	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	
A. DRUG SUBSTANCE	
B. **DRUG PRODUCT**[17, 18]	

[16] *Draft Guidelines for In Vivo Test Requirements for Second Entry Metered Dose Inhalers*, September, 1992.

[17] In addition to this data, product specific tests comparing the applicant' s product to the Canadian reference product should be submitted including: a) comparative chemical analysis to demonstrate equivalent qualitative and quantitative composition (relying in part, on published information on the reference product - e.g. product monograph, labels, CPS) and b) comparative physico-chemical tests including osmolality, surface tension, droplet size (using lase diffraction, Cascade impactor or multi-stage impinger).

[18] *Draft Guidelines for Metered Dose Inhalers*, November, 1992.

SECTION 1: TABLE 8
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7d
An injectable intended to be used as a solution

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics[19]	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	

[19]Comparative pharmacodynamic or clinical studies will be expected when the product cannot be demonstrated to have the same formulation or to be pharmaceutically equivalent to the reference product.

SECTION 1: TABLE 9
PRE-MARKET DATA ELEMENTS SUBGROUPS III-7d AND III-7h
An injectable not to be used as a solution and a rectal suppository that delivers the drug systemically

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
c. Other studies where applicable i.e. sensitization, irritation	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	

SECTION 1: TABLE 10
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7e
Peritoneal dialysis solutions

I GENERAL DATA ELEMENTS	
V CHEMISTRY AND MANUFACTURING REQUIREMENTS	
A. DRUG SUBSTANCE	
1. Pharmacopeial/ Reference Text Status	
8. Reference Standard	
9. Control Tests on the Drug Substance	
11. Packaging	
B. **DRUG PRODUCT**	
1. Pharmacopeial Status	
5. Formulation and Method of Manufacture	
6. Excipients	
7. Control Tests on the Finished Drug Product[20]	
9. Primary Packaging	

[20] Specifications and tests must include information to establish sterility and apyrogenicity.

SECTION 1: TABLE 11
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7f
Hemodialysis solutions

I GENERAL DATA ELEMENTS	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	
A. DRUG SUBSTANCE	
1. Pharmacopeial/ Reference Text Status	
8. Reference Standard	
9. Control Tests on the Drug Substance	
11. Packaging	
B. DRUG PRODUCT	
1. Pharmacopeial Status	
5. Formulation and Method of Manufacture	
6. Excipients	
7. Control Tests on the Finished Drug Product[21]	
8. Batch Analyses[22]	
9. Primary Packaging	
10. Stability	

[21] Apyrogenicity and sterility where applicable must be addressed.

[22] A certificate of analysis for one lot of the finished product must be submitted.

SECTION 1: TABLE 12
PRE-MARKET DATA ELEMENTS FOR SUBGROUP III-7g
An ophthalmic preparation

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics[23]	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS [24]	

[23]Comparative pharmacodynamic or clinical studies may be required to establish the relative safety and efficacy in relation to the reference product if pharmaceutical equivalence cannot be established.

[24]Evidence must be provided that the applicant's product and the reference product are the same or pharmaceutically equivalent.

SECTION 1: TABLE 13
PRE-MARKET DATA ELEMENTS FOR SUBGROUPS III-7i AND III-7j
Dermal topical, vaginal or nasal preparations for local effect and an otic preparation

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS[25]	

[25]Comparative pharmacodynamic or clinical studies may be required to establish the relative safety and efficacy in relation to the reference product if pharmaceutical equivalence cannot be established

SECTION 1: TABLE 14
PRE-MARKET DATA ELEMENTS SUBGROUPS III-7k
A dermal topical that delivers the drug systemically

I GENERAL DATA ELEMENTS	
III HUMAN STUDIES	
A. **CLINICAL PHARMACOLOGY**	
2. Pharmacodynamics	
IV CLINICAL STUDIES	
B. MAJOR STUDIES	
1. Short term studies	
a. Controlled studies	
c. Other studies where applicable i.e. irritation, sensitization	
V CHEMISTRY AND MANUFACTURING DATA ELEMENTS	

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DRUG SUBMISSION APPLICATION

The Drug Submission Application is designed to assist manufacturers and sponsors in submitting information required to initiate the evaluation of any one of the following types of submissions:

- Drug Identification Number (DIN) Application,
- New Drug Submission (NDS),
- Supplemental New Drug Submission (S/NDS)
- Notifiable Change (N/C) Submission,
- Cross Referenced to NDS or S/NDS (C/REF) Submission, or
- Investigational New Drug (IND) Submission.

Form A is to be completed for all submission types. Only one formulation and formulation strength should be included per copy of this form.

If this form has been previously completed and a Project ID number assigned, additional or supplementary information for a submission need only be accompanied by a covering letter that includes:

- the drug name(s)
- the Project ID number
- whether the information was requested by Therapeutic Products Directorate, and
- a brief description of the attached information

Form B, C, D, or E is to be completed in addition to Form A, depending on the type of submission. DIN Applications require only the completion of Form A.

Completion Instructions for Form A may be found by turning the complete forms package over. Completion instructions for specific submission types (Forms B, C, D, E) may be found at the bottom of each form.

All shaded fields are for Health Protection Branch (HPB) use only.

FORM A - GENERAL INFORMATION

PART 1 - Manufacturer / Sponsor Information

1. Type of Submission	2. Number of Volumes	**HPB Use Only:**	3. Project ID	4. Category	5. Status

Manufacturer / Sponsor

6. Code	7. Name

8. Street No. and Name	9. City/Town	10. Prov./State	11. Country	12. Postal/ZIP Code

Contact Person

13. Name	14. Title	15. Tel. No.	16. FAX No.	17. Language ☐ English Preferred ☐ French

Mailing Address ☐ Same as above ☐ See below

18. Street No. and Name	19. City/Town	20. Prov./State	21. Country	22. Postal/ZIP Code

Canadian Distributor ☐ Same as ☐ Same as Mailing ☐ See below

manufacturer/sponsor	Address
23 Name	

24. Street No. and Name	25. City/Town	26. Prov	27. Country	28. Postal Code

Other Name and Address on Label

29. Name

30. Street No. and Name	31. City/Town	32. Prov./State	33. Country	34. Postal/ZIP Code

Responsible Bureau (HPB Use Only)

35. Code	36. Name	37. Code	38. Name

39. CR Date (D / M / Y)	40. CR File No.	41. Prov./State	42. Kit ☐Yes ☐No	43. Parent ID No.

44. Product Name	45. Name Type	46. Schedule

47. Proper or Common Name

48. Related Submissions (referred to in this submission)

Type	Project ID No.	Product Name	Manufacturer / Sponsor Name	Notes

HPB 3011 (3-91)

PART 2 - Formulation Information on this Submission

49. Proposed Expiry / Shelf Life ___ years _____ months

50. Medicinal Ingredients

Ingredient Name	Standard	Strength	Units	Pe	Calculated as Base?
					☐ Yes ☐ No
					☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

Attach separate sheets (same format) if necessary. Number of pages attached: _____

51. Non-medicinal ingredients (include colouring agents)

Ingredient Name	Standard	Strength	Units	Per

Attach separate sheets (same format) if necessary. Number of pages attached: _____

52. Specify the dosage form

53. Package Sizes available

54. Therapeutic Classification

55. Specify the Route(s) of administration

56. Use of Drug ☐ Human ☐ Veterinary Use (see 60 - 62)

☐ General Disinfectant (inanimate objects only) ➢ ☐ hospital ☐ food processing ☐ instruments

57. Recommended Purpose

58. Recommended Dosage

59. Draft of Proposed Canadian Label and Package Insert enclosed? ☐ Yes ☐ No

Complete for Veterinary Products only

60. Species Recommended for use

_____

_____

_____

61. Used for treatment of food-producing animals ☐ Yes ☐ No

62. Withdrawal Time

Species	Days	Hours

63. Name of Authorized Signing Official	64. Title	65. Signature	66. Date D	M	Y

SECTION 2: POST-APPROVAL REPORTING SCHEDULES AND REQUIREMENTS, PRODUCT ASSESSMENT, PRODUCT/SUBSTANCE RE-ASSESSMENT, AMENDMENT OF REPORTING SCHEDULES

SECTION 2:POST-APPROVAL REPORTING SCHEDULES AND REQUIREMENTS, PRODUCT ASSESSMENT, PRODUCT/SUBSTANCE RE-ASSESSMENT, AMENDMENT OF REPORTING SCHEDULES

2.1Introduction

This second component of the Product Licensing Framework describes in detail the post-approval activities including reporting schedules and requirements, product assessment, product/substance re-assessment and amendment of reporting requirements.

Upon completion of the pre-market review, a favourable benefit/risk ratio will result in the issuance of a product licence and one of three (schedule A, B or C) post-approval reporting schedules. The reporting schedules are differentiated on the basis of potential risk posed by the drug product as defined by the level of concern and uncertainty about the safety of the drug product in the market place and on the potential or actual risks identified about the product during the review process. Within this scheme a new active substance for which there is no available data on safety in the market place, will have a higher level of concern and uncertainty and will likely receive schedule A reporting requirements when licensed to market. Schedule A requirements will ensure that the product receives close scrutiny for safety during the first three years on the Canadian market. Similarly, a drug product with a hepatotoxicity concern identified during the review process but for which the benefit/risk warrants market authorization, may also be licensed with a schedule A reporting requirement and receive a high level of scrutiny. At specified times, as experience is gained on the safety of the product in the market place, periodic re-assessment of the drug product/substance and its reporting requirements will occur. A favourable review will facilitate the reduction in level of post-approval safety reporting and scrutiny. When the drug product has sufficient market safety experience and demonstrated that safety issues can be effectively managed, or when there are negligible safety issues, the product will receive a reporting schedule with a reduced level of post-approval reporting and scrutiny.

The post-approval reporting requirement is comprised of the Periodict Safety Update Report (PSUR) with the same format and content agreed upon at the International Conference on Harmonization (see Appendix 2, ICH document E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs). Sponsors should refer to this ICH document to ensure the post-approval reports are prepared in the comprehensive detail dictated by ICH. The PSUR will replace current annual ADR reporting for products with schedule A and B reporting requirements. For schedule C reporting, the report will be a modified version of the PSUR with primary focus on the safety issue in question.

Consistent with the intent of the ICH document, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR from

a sponsor. Accordingly, the PSUR for some active substances, will cover several drug products from a single sponsor. Where applicable, cross referencing of reports is encouraged. In addition, poison and misuse information will also be required as a component of the post-approval assessment.

Sponsors should note that the approach summarized above is consistent with regulatory approaches in the U.S. and Europe (see Appendix 3 for comparisons).

The post-approval Product Status Report on chemistry and manufacturing changes (described in section 2.3.5.2) will not be part of the reporting requirement. However, sponsors of products with schedule A or B reporting will continue to prepare annual status reports and maintain them on site to facilitate establishment licence inspection.

When reading through this Section 2 of the document, it should be kept in mind that there is no direct relationship between the pre-market drug category and the reporting schedule. For example, a drug product that was submitted as Category IV (high risk) pre-market submission, may have demonstrated a sufficient safety profile and market history in another jurisdiction such that close post-approval scrutiny is not warranted. Accordingly, such a product may be considered for a less stringent reporting schedule upon initial licence approval in Canada.

2. 2International Birth Date

Consistent with general principles outlined at ICH (Appendix 2), the Therapeutic Products Programme has adopted the international birth date (date of first approval by a regulatory authority) as the standard "starting point" for the submission of information on a drug product under the post-approval assessment scheme. The manufacturer's data base will be frozen for the active substance every 6 months subsequent to the birth date during the initial years of marketing. Thus all drugs will have official data lock-points at 6 month intervals. This standardization within the drug licensing process will facilitate the coordination and evaluation of information at the national and international level.

2.3Reporting Requirements

2.3.1Reporting Schedules and Requirements, Product/Substance Re-assessment and Amendment of Reporting Schedules

Table 1 (following) details all the post-approval activities following issuance of a product licensing including; reporting schedules, required reports, product/substance re-assessment and

amendment of reporting requirements. Sponsors will be expected to monitor their products in accordance with the requirements of the reporting schedule assigned to their product.

Section 2 Table 1: Reporting Schedule, Required Reports and Frequency; Product/Substance Re-assessment

LICENCE	Reporting Schedule	Required Safety Report	Reporting Frequency - Preparation - Submission	ADR Reporting	Product/ Substance Re-assessment
	A	PSUR	- prepare every 6 months - submit annually or when monitoring identifies concern or when requested by TPP	continue to submit serious and unexpected ADR's as per current regulations PSUR to replace current annual reports	3 yr
	B	PSUR	- prepare annually - submit only on request or when monitoring identifies concern		5 yr
	C	Upon identification of issue of concern .	- prepare and submit report within 30d of	Continue annual reports as per	

		sponsor will submit modified or truncated version of PSUR with focus on issue under investigation	request by TPP	current Schedule 844 requirements - summary line listing - critical analysis - evaluation of recommended actions	-

Effectiveness data to be submitted on request (see below for details)
Sponsors to notify and report on specific issues of concern (see below for details)

2.3.1.1 Effectiveness Data

Drug products are approved primarily on the basis of efficacy data gathered from controlled clinical trials. Under some specialized circumstances, a drug may be approved on the basis of surrogate markers. It is now well recognized that the therapeutic outcome in a real world patient population (effectiveness) may differ from efficacy determined in clinical trials or via surrogate markers. Accordingly, effectiveness issues may arise only when the drug product is widely marketed and as as a result there may be times when requests for effectiveness studies are warranted. Within the product licensing framework, there will be provision for the TPP to request effectiveness data.

The following conditions may prompt a request for effectiveness data:

1.A drug product licensed on the basis of surrogate makers and effectiveness needs to be validated (i.e. product with a Conditional Licence)

2.Post-approval ADR reports indicate potential lack of efficacy

3.A product is licensed with weak evidence of efficacy

2.3.1.2 Notification and Reporting on Specific Issues of Concern

In addition to the reporting requirements outlined above, sponsors will be required to:

a)Notify the Therapeutic Products Programme within 5 days when, on basis of safety or quality concerns, an expert panel or advisory committee has been struck to address an issue or when there has been significant regulatory action in another jurisdiction including direction to issue warnings, health advisory or the removal of a product from the market.

b) Prepare and submit a report on the issue that prompted the notification on activities in another regulatory jurisdiction. The report should be available to the TPP within 30 days of the notification. The 30 day timeframe may be subject to negotiation with the TPP when

the scope of the safety issue under investigation warrants additional time to gather the necessary information.

c) Prepare and submit a report within 30 days of request by the TPP when a signal/alert is raised in Canada. As per item b) above, the timeframe may be subject to negotiation with the TPP.

It is the intention of the Therapeutic Products Programme to continue to expand the Spontaneous Adverse Drug Reaction Monitoring Program and sponsors will continue to submit adverse drug reaction reports for serious and unexpected drug reactions as per current regulations and international agreement.

At specified intervals (3 years and 5 years respectively, for products with A or B reporting schedules) the Therapeutic Products Programme will conduct a product/substance re-assessment. For these purposes the sponsor will prepare a Summary Report covering the entire time of the assigned reporting schedule (3 years for Schedule A and 5 years for Schedule B). The format and content of the Summary Report to be submitted for re-assessment has not yet been defined. This issue is under discussion internationally and is likely to be resolved by the time the licensing scheme is implemented. Canada intends to harmonize with the format and content of the Summary Report developed at the international level.

2.3.2Schedule A Reporting

Sponsors of drug products that receive schedule A reporting requirements will be expected to fulfil the following:

Data Elements

Safety Report (PSUR)- prepared every 6 months submitted annually or when monitoring identifies concern
Product/Substance Re-assessment - Summary report at 3 years

Safety Report

This report will contain information on the safety, use, marketing and continuing development of the drug product. It will be composed of:

Periodic Safety Update Report[1] (PSUR)
Poison reports and misuse information.

Sponsors will prepare the Safety Reports **every six months** within the time period specified by international agreement (60 days). The international birth date of the drug product is the date for the preparation and submission of these reports.

The report will be submitted to the Therapeutic Products Programme annually, when monitoring identifies issues of concern or, when required by the Therapeutic Products Programme.

Product/Substance Re-assessment

A comprehensive re-assessment of the product/substance will occur at 3 years. A favourable review will facilitate movement to a less stringent reporting schedule (see licence status below). At that time, a summary report will be submitted for review.

2.3.3Schedule B Reporting

Sponsors of drug products that receive schedule B reporting requirements will be expected to fulfil the following:

Data Elements

Safety Report (PSUR) - prepare annually, submit on request or when monitoring identifies concerns **Product/Substance Re-assessment** - summary report at 5 years

Safety Report

This report will contain information on the safety, use, marketing and continuing development of the drug product. It will be composed of:

Periodic Safety Update Report (PSUR)
Poison reports and misuse information.

Sponsors will prepare the Safety Reports **annually** within the time period specified by international agreement (60 days). Where applicable, the international birth date of the drug product is accepted as the date for the preparation and submission of the report.

The report will be submitted **on request** from the Therapeutic Products Programme or **when a product/substance re-assessment** is scheduled. In addition, the reports must be submitted **when issues of concern become apparent** to the sponsor during the monitoring period.

Product/Substance Re-assessment

The product/substance re-assessment for products with schedule B reporting will occur every 5 years (see licence status below). At that time, a summary report will be submitted for review.

2.3.4Schedule C Reporting

Drugs falling within this group will **not** be required to routinely prepare PSURs. However, sponsors will continue to monitor their products and prepare annual ADR reports to be kept on file according to the requirements of Schedule 844. As per current practice, these reports will not

be routinely submitted to the TPP. When information becomes available indicating possible problems with safety, quality or effectiveness, sponsors will be required to submit within 30 days of request by the TPP, a truncated version of the PSUR focusing on the issue under investigation. Dependent on the scope of the issue, there may be occasions when the TPP will consider negotiating an alternate timeframe for report preparation.

In addition, it will be the responsibility of sponsors to initiate dialogue with the TPP and send in reports when they note significant safety, quality or effectiveness issues during the annual monitoring activity.

2.3.5Post-Approval Reports

Dependent on the post-approval reporting schedule (type A, B or C) or when quality, safety or effectiveness concerns are noted, the sponsor may need to prepare and submit one or more of the following reports:
a)Periodic Safety Update Report (PSUR)
b)Adverse Drug Reaction (ADR) report
c)Summary Report for product/substance re-assessment
d)Product Status Report (to be kept on site).

2.3.5.1Periodic Safety Update Report (PSUR)[26]

A copy of the Periodic Safety Update Report[26] is attached as Appendix 2, ICH document E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. The content of this safety report has been the subject of international discussion and has been agreed upon at ICH. Sponsors should refer to the appended ICH document to ensure that the safety report for their product is completed in the comprehensive manner required. In addition to the PSUR, misuse and poisoning data will complete the reporting requirements for a drug product within the licensing framework.

2.3.5.2Adverse Drug Reaction (ADR) Report

This report will be prepared by sponsors with drug products which have a type C post approval reporting schedule. The report will be a truncated version of the PSUR report with focus on the issue under investigation including critical analysis and evaluation of recommended actions. Sponsors should refer to the *Guidelines for Reporting Adverse Reactions to Marketed Drugs* for guidance on the format and necessary information to be included in the report.

2.3.5.3Product/Substance Summary Report

Sponsors with drug products in type A or B reporting schedules will prepare a Product/Substance Summary Report at times specified (3 years for type A and at 5 years for type B). The report will cover the entire previous reporting period (3 or 5 years respectively, for schedule A or schedule B products). The format and content of the Product/Substance Summary Report has not yet been defined. This issue is under discussion internationally and is likely to be resolved by the time the licensing scheme is implemented. Canada will harmonize with the content and format for this report when it is finalized at the international level.

It is recognized that several sponsors may be marketing the same active substance as drug

[26]Previously referred to as CIOMS II (Council for International Organizations of Medical Sciences) and currently incorporated into ICH document E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. The PSUR information has been abstracted from the ICH document.

products and that there is potential for overlap in submitted drug substance information during product/substance re-assessment. However, drug products with the same active ingredient from different sponsors are usually not identical and may have unique ADR profiles. Within the drug licensing framework, all sponsors will be responsible for generating safety reports and product/substance summary reports for their own products. This, however, does not preclude arrangements between sponsors to co-operate in the generation of information on the active substance.

2.3.5.4Product Status Report

For products with Type A or B reporting schedules, a product status report will be prepared annually and kept on site to facilitate inspection for establishment licences. Schedule D products may be required to submit these reports to the Bureau of Biologics and Radiopharmaceuticals to monitor products and assign appropriate lot-testing. The report is not required to be submitted for licence renewal or amendment. Products with a Type C licence will not be required to prepare a Product Status Report.

The report will describe changes to the drug product since the last Product Status Report and provide information on the quality of the drug product, including:

•All changes subject to Record and (Annual) Notice of Change and Record of Change[27] made to the information required in Section V, *Chemistry and Manufacturing Requirements* of the drug submission; and

•A summary critique that discusses the significance of issues related to product quality and equivalence to the drug product originally licensed, including:

a) all product complaints;
b) all failures of any lot[28] of the product, whether marketed or not, to meet both in-process requirements and final product specifications;
c) anomalies in test results for both in-process and final product that lead to investigations by the sponsor;
d) corrective actions taken to address the above complaints, failures and anomalies.

The sponsor's senior executive officer in Canada must certify the Product Status Reports for

[27]Changes are described in Schedule 733. As per the requirements in the schedule, some changes are subject to immediate information submission requirements.

[28]In the case of drugs listed on Schedule D to the Food and Drugs Act (Biologicals), certificate of analysis submission for review or actual production lot samples may be required for examination.

accuracy and completeness of the information.

2.4Licence Status

2.4.1Annual Licence Renewal

The Therapeutic Products Programme will implement an annual licence renewal system. This will be a paper exercise and will replace the annual DIN renewal. The issuance of the licence will be subject to fulfilment of the applicable regulatory requirements. Sponsors can assume that the licence/authorization **will be renewed annually** unless:

- Reporting requirements are not met;
- GMP and other regulatory requirements including fee requirements are not met; or
- Problems identified during post-market assessment cannot be resolved.

Future regulations will give the Therapeutic Products Programme **the authority to not renew** a drug product licence if the sponsor fails to meet the above requirements or other regulatory requirements. Where warranted, drug products may be made available to specified individuals through the Special Access Program while the licence renewal issues are being resolved.

2.4.2Suspension/Revocation/Amendment of a Drug Product Licence

The Therapeutic Products Programme will have the authority to suspend, revoke or amend licence requirements for drug products prior to the licence expiration date should public health concerns become apparent. Some examples of such issues would include:

i) evidence of lack of potency
ii) GMP concerns such as contamination
iii) significant safety or effectiveness concerns

Where warranted, drug products may continue to be made available to specified individuals through the Special Access Program while the licencing concerns are being resolved.

2.4.3Product/Substance Re-assessment

At the time of the periodic licence type review, the Therapeutic Products Programme will do a comprehensive assessment of the submitted data to determine if the original benefit-risk analysis remains valid. As noted previously, the format and content of the required summary report is currently under discussion internationally and will be further defined once international agreement is reached. The product/substance re-assessment will include a review of the product through the previous reporting schedule as well as a determination of the reporting schedule

required to continue sale of the drug product. If the licence holder has presented information that alters the validity of the original benefit/risk assessment, the licence holder may have to make changes to the product, product labelling or other parameters before the Programme can re-issue the licence. Based on the outcome of the review, a decision will be made as to whether the reporting schedule should be retained or amended to reduce or increase the reporting requirements.

2.4.4Multiple Product (Class, Group) Assessment

Based on the drug product safety profile or from signals arising form post-approval surveillance, or from safety issues arising from the product/substance re-assessment, there may be times when an entire group of drug products may be warranted. Within PLF, this grouping of drug products is intended to be highly flexible and will vary with specific concerns. In some instances, the same pharmacological grouping would be appropriate. In other cases the group may be composed of products within the same therapeutic class, chemical group or all products used for a particular indication. The intent of a group assessment would focus on reviewing the appropriate group of products that are relevant to a particular safety issue. Group assessments and how to resolve issues of confidentiality of proprietary information and generation of necessary data is currently under discussion and will be further defined.

2.4.4.1Product Monograph Changes

Within the PLF, based on the outcome of a group assessment, the TPP will have the authority to require the same statements in all Product Monographs relating to the safety issue which prompted the group assessment.

3.0SUMMARY

3.1The Licensing Process

Table 3.1 (following), summarizes the entire continuum of the licensing process which was described in Sections 1 and 2 of this document. The roles of the drug sponsor and Therapeutic Products Programme are outlined to facilitate a clear understanding of how a drug product will be evaluated within the product licensing scheme.

3.2 Appeals Process

As per current practices, it is the intent of the Therapeutic Products Programme to include an appeals process on many aspects of activities proposed in the Product Licensing Framework.

Table 3.1

APPENDICES

APPENDIX 1:

The Biopharmaceutics List

The Biopharmaceutics List

The Therapeutic Products Programme is in the process of creating the Biopharmaceutics List. Initially, the list will be based on:

•drugs currently requiring the submission of an Abbreviated New Drug Submission (ANDS);

•drugs which would require comparative bioavailability studies as defined in the Final Report, D-09; Drug Identification Number, September 1994;

•all NAS as they receive a notice of compliance

Other factors regarding the Biopharmaceutics List:

•listing of an ingredient will not be dependent on the ingredient being on a federal schedule;

•the criteria in the Final Report, D-09: Drug Identification Number, September 1994, remain valid and will form the framework for decisions for listing;

•the Therapeutics Products Programme will consult with stakeholders on the initial list;

•an ingredient will remain on the list unless a sponsor petitions for its removal. An advisory panel convened by the Therapeutic Products Programme will review the petition. The Programme will publish the agenda of the advisory panel in advance, permit additional parties to submit data in support of or against the petition, and hold meetings that would be open to the public; and

•the Therapeutic Products Programme will make the list available through the Bulletin Board for screening and evaluation.

APPENDIX 2:

ICH Harmonized Tripartite Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Harmonized Tripartite Guideline

CLINICAL SAFETY DATA MANAGEMENT:

PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

Recommended for Adoption
at Step 4 of the ICH Process
on 6 November 1996
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

ICH Harmonised Tripartite Guideline
Having reached *Step* 4 of the ICH Process at the ICH Steering Committee meeting on 6 November 1996, this guideline is recommended for adoption to the three regulatory parties to ICH

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CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

1. INTRODUCTION

1.1 Objectives of the Guideline

The main objective of ICH is to harmonize technical requirements for registration or marketing approval. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (KU, Japan, USA). In order to avoid duplication of effort and to ensure that important data are submitted with consistency to regulatory authorities, this guideline on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed.[29]

1.2 Background

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization. Surveillance of marketed drugs is a shared responsibility between Regulatory Authorities and Marketing Authorization Holders (MAH). They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

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29 [29]Guidelines are not legally binding. Some portions of this guideline may not be reflected in existing regulations. To that extent, until the regulations are amended, MAHs must comply with existing regulations.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product at defined times post-authorization, in order to:

- report all the relevant new safety information from appropriate sources
- relate these data to patient exposure
- summarize the market authorization status in different countries and any significant variations related to safety
- create periodically the opportunity for an overall safety reevaluation
- indicate whether changes should be made to product information in order to optimize the use of the product.

However, if the PSURs required in the different countries where the product is on the market require a different format, content, period covered and filing date, MAH would be required to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonize the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The US regulations require quarterly reports during the first 3 years, then annual reports. The FDA has recently published proposed rules[30] which take into account the CIOMS Working Group II proposals[31].

- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.

- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorization. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabeled must be reported every 6 months for 3 years and annually thereafter.

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[30] Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, Federal Register, 27 October 1994, pp. 54046-54064.

[31] [31] International Reporting of Periodic Drug-Safety Update Summaries. Final Report of CIOMS Working Group II. CIOMS - Geneva 1992

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented. Appended is a glossary of important relevant terms.

1.3 Scope of the Guideline

This guideline on the format and content of periodic safety update reports (PSURs) is considered particularly suitable for comprehensive reports covering short periods (e.g. six months, one year) often prepared during the initial years following approval/authorization.

This guideline might also be applicable for longer term reporting intervals; however, other options may be appropriate.

1.4 General Principles

1.4.1 One report for one active substance

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g. children vs. adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

1.4.2 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals, as well as data on serious, unlisted ADRs (see 1.4.5), which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of lifethreatening conditions, may represent a significant hazard, and in that sense be a "safety issue". Although these types of cases should not be included with the usual ADR presentations (i.e., line-listings and summary tabulations), such findings should be discussed within the PSUR (see section 2.8), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as

relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change(e.g., population exposed, duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, these data should be included and discussed in the PSUR, even if it is known that they are included in another company's PSUR.

1.4.4 International birthdate and frequency of review and reporting

Each medicinal product should have as an International Birth Date (IBD), the date of the first marketing authorization for the product granted ~ to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorization for any of the various authorizations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cut-off for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorizations at different times in different countries; it is during this early period that harmonization of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept six-monthly PSURs or PSURs based on multiples of six months. Therefore, preparation of PSURs for all regulatory authorities should be based on data sets of six months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial one for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g., children vs. adults; prescription to non-prescription status). The potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting.

The MAH should submit a PSUR within 60 days of the data lock point.

1.4.5 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet"(CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already Listed or is still Unlisted, terms which are introduced to distinguish them from the ususal terminology of "expectedness" or "labeledness" which is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.

1.4.6 Presentation of data on individual case histories

Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

a) Direct reports to MAH (or under MAH control):
- Spontaneous notifications from health care professionals
- Spontaneous notifications from non-health care professionals or from consumers (non-medically substantiated)
- MAH-sponsored clinical studies[32] or named-patient ("compassionate") use

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32 [32]What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between

b) Literature

c) ADR reporting systems of regulatory authorities

d) Other sources of data:
- reports on ADRs exchanged between contractual partners (e.g., licensors, licensees)
- data in special registries, such as maintained in organ toxicity monitoring centers reports created by poison control centers
- epidemiologic data bases

Description of the reaction
Until an internationally agreed ICH coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company

Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make available on request, the "verbatim" information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable)

- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data

- if a MAH disagrees with a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data

- MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis

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spontanewous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH's medical interpretation (identified by asterisk or other means).

Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see 1.4.6a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see 1.4.6d) might not be (1) possible without standardization of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non-serious listed ADRs). Details are found in section 2.6.4.

2. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR)

The following sections are organized as a sample PSUR. In each of the sections, guidance is provided on what should be included.

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: (PRODUCT)

MAHs NAME AND ADDRESS (Corporate headquarters or other company entity responsible for report preparation)

PERIOD COVERED BY THIS REPORT: (dates)

INTERNATIONAL BIRTH DATE: Date (Country of IBD)

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

TABLE OF CONTENTS FOR MODEL PSUR

Introduction

World-wide market authorization status

Update of regulatory authority or MAH actions taken for safety reasons

Changes to Reference Product Information

Patient exposure

Presentation of individual case histories .

Studies

Other information.

Overall safety evaluation

Conclusion

APPENDIX: COMPANY CORE DATA SHEET.

2.1 Introduction

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see 1.4.6), the possibility of data duplication should be noted.

2.2 World-wide Market Authorization Status

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorization, and subsequent renewal;

- any qualifications surrounding the authorization, such as limits on indications if relevant to safety;

- treatment indications and special populations covered by the market authorization, when relevant

- lack of approval, including explanation, by regulatory authorities;

-withdrawal by the company of a license application submission if related to safety or efficacy

- dates of launch when known

- trade name(s).

Typically, indications for use, populations treated (e.g., children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorizations. For multiple authorizations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorization date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organized. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 Update of Regulatory Authority or MAH Actions Taken for Safety Reasons

This section should include details on the following types of actions relating to safety t.hat. were taken during the period covered bv the report and between data lock-point and report submission:

- marketing authorization withdrawal or suspension
- failure to obtain a marketing authorization renewal
- restricions on distribution
- clinical trial suspension
- dosage modification
- changes in target population or indications
- formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 Changes to Reference Safety Information

The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference document (CCDS) may contain more "listed" information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

2.5 Patient Exposure

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognized that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs. adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (withlocally recommended daily dose) or other sebmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

2.6 Presentation of Individual Case Histories

2.6.1 General considerations

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.

With regard to the **literature,** MAHs should monitor standard, recognized medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what "primary source" is given a case, if there is a publication, it should be noted and the literature citation given.

In some countries, there is no requirement to submit **medically unconfirmed pontaneous reports** that originate with consumers or other non-health care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications

- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use

- all serious reactions, and non-serious unlisted reactions, from the literature

- all serious reactions from regulatory authorities

Collection and reporting of non-serious, **listed ADRs** may not be required in all ICH countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

2.6.3 Presentation of the line listing

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g., weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the linelistings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number

- Country in which case occurred

- Source (e.g., clinical trial, literature, spontaneous, regulatory authority)

- Age and sex

- Daily dose of suspected drug (and, when relevant, dosage form or route)

- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).

- Dates of treatment. If not available, best estimate of treatment duration.

- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See Section 1.4.6 for guidance.

- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.

- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s), dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, listed, spontaneously reported reactions (see also 2.6.2).

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from Other

Sources (see 1.4.6c) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.
When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in the table(s) or as a narrative.

2.6.5 MAH, Analysis of Individual Case Histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (Section 2.9).

2.7 Studies

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

2.7.1 Newly analyzed company-sponsored studies

All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2 Targeted new safety studies planned, initiated or continuing during the reporting period.

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PSUR as described under 2.7.1.

2.7.3 Published safety studies

Reports in the scientific and medical literature, including relevant published abstracts from

meetings, containing important safety findings (positive or negative) should be summarized and publication reference(s) given.

2.8 Other Information

2.8.1 Efficacy-Related Information

For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2 Late-Breaking Information

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 2.9).

2.9 Overall Safety Evaluation

A concise analysis of the data presented, taking into account any late-breaking information (Section 2.8.2.), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- a change in characteristics of listed reactions, e.g. severity, outcome, target population

- serious unlisted reactions, placing into perspective the cumulative reports

- non-Serious unlisted reactions

- an increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- drug interactions

- experience with overdose, deliberate or accidental, and its treatment

- drug abuse or misuse

- positive or negative experiences during pregnancy or lactation

- experience in special patient groups (e.g., children, elderly, organ impaired)

- effects of long-term treatment.

2.10 Conclusion

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);

- specify and justify any action recommended or initiated.

APPENDIX: COMPANY CORE DATA SHEET

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

3. GLOSSARY OF SPECIAL TERMS

Company Core Data Sheet (CCDS)
A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)
All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date)
The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

International Birth Date (IBD)
The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

Listed Adverse Drug Reaction
An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

Spontaneous Report or Spontaneous Notification
An unsolicited communication to a company, regulatory authority or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

Unlisted Adverse Drug Reaction
An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.

- Table 1 -

EXAMPLE OF PRESENTATION OF WORLD WIDE MARKET AUTHORIZATION STATUS

Country	Action Date	Launch Date	Trade Name(s)	Comments
Sweden	A-7/90 AR-10/95	12/90 -	Bacteroff -	- -
Brazil	A-10/91 A-1/93	2/92 3/93	Bactoff Bactoff - IV	- IV dosage form
United Kingdom	AQ-3/92 A-4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (>65) excluded (PK) Topical cream
Japan	LA-12/92	-	-	to be refiled
France	V-9/92	-	-	Unrelated to safety
Nigeria	A-5/93 A-9/93	7/93 1/94	Bactoff Bactoff	- -
Etc.				

Abbreviations for Action: A= authorized; AQ=authorized with qualifications; LA lack of approval; V=voluntary marketing application withdrawal by company; AR=Authorization renewal

- Table 2 -

PRESENTATION OF INDIVIDUAL CASE HISTORIES

(See 2.6.2 and 2.6.4 for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH			
- spontaneous ADR reports*	S	-	+
	NS U	-	+
	NS L**	+	-
- MAH sponsored studies	SA	-	-
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
- regulatory authorities	S	-	+
- contractual partners	S	+	-
- registries	S	+	-

** Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.*

*** Line listing shoud be provided as PSUR addendum only on request by regulatory authorities.*

S=serious; L=listed; A=attributable to drug (by investigator or sponsor); NS=non-serious; U=Unlisted

-Table 3 -

(EXAMPLE OF SUMMARY TABULATION)#
NUMBER OF REPORTS BY TERM (SIGNS, SYMPTOMS AND DIAGNOSES) FROM SPONTANEOUS (MEDICALLY CONFIRMED), CLINICAL STUDY AND LITERATURE
CASES: ALL SERIOUS REACTIONS

(An * indicates an unlisted term)

Body system/ ADR term	**Spontaneous/ Regulatory bodies**	**Clinical trials**	**Literature**
CNS			
hallucinations*	2	0	0
etc.			
etc.			
_____	_____	_____	_____
Sub-total			
CV			
etc.			
etc.			
_____	_____	_____	_____
Sub-total			
Etc.			
Total			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g , x-spontaneous/regulatory, y-clinical study, and z-literature cases)

 # This table is only one example of different possible data presentations which are at the discrtion of the MAH (e.g., serious and non-serious in the same table or as separate tables, etc.)

APPENDIX 3:

International Comparison of Post Approval Requirements for Product Safety Reporting

International Comparison of Post Approval Requirements for Safety Reporting*

	United States		Europe		Canada	
	Current	**Within ICH**	**Current**	**Within ICH**	**Current**	**Within PLF**
Type of Report	**Safety**	**PSUR**	**Safety**	**PSUR**	**ADR Report**	**PSUR**
Content	•summary & analysis of serious & unexpected reports •line listing of other reports •history of Adverse Event related actions •new clinical & toxicology studies	•content & format as per ICH document direction	•detailed record of all suspected Adverse Events •scientific /clinical safety evaluation	•content & format as per ICH document direction	•summary line listing of all ADRs •critical analysis •evaluation and any recommended actions	**•content & format as per ICH document direction**
Frequency of Reporting	•quarterly for 3 years •annually thereafter	•decision not final	•varies country to country	•every 6 months for 2 years •annually for 3 years •summary report every 5 years	•prepare annually for all products •submit on request	**Schedule A** •prepare every 6 mos •submit annually for 3 years •summary report at 3 years **Schedule B** •prepare annually •submit summary report at 5 years **Schedule C** •as per current ADR requirements

* table does not address expedited reporting required in all jurisdictions